Harris, A.
09/763370

- key terms

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     (FILE 'REGISTRY' ENTERED AT 12:07:00 ON 21 MAY 2001)
L1          267 SEA FILE=REGISTRY ABB=ON  PLU=ON  (OSTEOCALCIN ? OR
                DEOXYPYRIDINOLINE OR ALKALINE PHOSPHATASE ? OR "PHOSPHATA
                SE, ALKALINE"?)/CN

     (FILE 'CAPLUS' ENTERED AT 12:08:27 ON 21 MAY 2001)
L1          267 SEA FILE=REGISTRY ABB=ON  PLU=ON  (OSTEOCALCIN ? OR
                DEOXYPYRIDINOLINE OR ALKALINE PHOSPHATASE ? OR "PHOSPHATA
                SE, ALKALINE"?)/CN
L2        64725 SEA FILE=CAPLUS ABB=ON  PLU=ON  L1 OR ICTP OR ALP OR
                PICP OR PINP OR OSTEOCALCIN OR OSTEO CALCIN OR BALP OR
                DEOXYPYRIDINOLINE OR DEOXY PYRIDINOLINE OR TERMIN?(W)(PRO
                PEPTIDE OR TELOPEPTIDE OR (PRO OR TELO)(W)PEPTIDE) OR
                ALKAL? PHOSPHATASE OR (TYPE(W)(1 OR I))(3A)COLLAGEN
L3         7046 SEA FILE=CAPLUS ABB=ON  PLU=ON  BONE(5A)(METAST? OR
                CANCER? OR CARCIN? OR TUMOUR OR TUMOR OR NEOPLAS?)
L4          436 SEA FILE=CAPLUS ABB=ON  PLU=ON  L3(5A)(DIAGNOS? OR
                DETERM? OR DETECT? OR DET## OR SCREEN?)
L5           26 SEA FILE=CAPLUS ABB=ON  PLU=ON  L4 AND (OSTEOBLAST? OR
                OSTEOCLAST? OR OSTEO(W)(BLAST? OR CLAST?))
L6           10 SEA FILE=CAPLUS ABB=ON  PLU=ON  L2 AND L5


L1          267 SEA FILE=REGISTRY ABB=ON  PLU=ON  (OSTEOCALCIN ? OR
                DEOXYPYRIDINOLINE OR ALKALINE PHOSPHATASE ? OR "PHOSPHATA
                SE, ALKALINE"?)/CN
L2        64725 SEA FILE=CAPLUS ABB=ON  PLU=ON  L1 OR ICTP OR ALP OR
                PICP OR PINP OR OSTEOCALCIN OR OSTEO CALCIN OR BALP OR
                DEOXYPYRIDINOLINE OR DEOXY PYRIDINOLINE OR TERMIN?(W)(PRO
                PEPTIDE OR TELOPEPTIDE OR (PRO OR TELO)(W)PEPTIDE) OR
                ALKAL? PHOSPHATASE OR (TYPE(W)(1 OR I))(3A)COLLAGEN
L7          9918 SEA FILE=CAPLUS ABB=ON  PLU=ON  BONE(S)(METAST? OR
                CANCER? OR CARCIN? OR TUMOUR OR TUMOR OR NEOPLAS?)
L8          1017 SEA FILE=CAPLUS ABB=ON  PLU=ON  L7(S)(DIAGNOS? OR
                DETERM? OR DETECT? OR DET## OR SCREEN?)
L9            78 SEA FILE=CAPLUS ABB=ON  PLU=ON  L8 AND (OSTEOBLAST? OR
                OSTEOCLAST? OR OSTEO(W)(BLAST? OR CLAST?))
L10           20 SEA FILE=CAPLUS ABB=ON  PLU=ON  L2 AND L9

L11           20 L6 OR L10


L11  ANSWER 1 OF 20  CAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2001:218659  CAPLUS
TITLE:                    Expression of molecular markers for bone
                          formation increases during experimental acute
                          otitis media
AUTHOR(S):                Melhus, Asa; Ryan, Allen F.
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CORPORATE SOURCE: Department of Surgery/Otolaryngology, University of California at San Diego School of Medicine and Veterans Affairs Medical Center, La Jolla, CA, USA
SOURCE: Microb. Pathog. (2001), 30(3), 111-120
CODEN: MIPAEV; ISSN: 0882-4010
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bony tissues are integral parts of the function of the middle ear and the protection of adjacent vital structures. To explore the reaction of middle ear bone to acute otitis media, rats were challenged with Streptococcus pneumoniae and Haemophilus influenzae. Local changes were monitored for up to 1 mo. After reverse transcription, competitive polymerase chain reaction was used to **det**. the expression levels of two mol. markers of **bone** formation, **osteocalcin** and procollagen I, and the two cytokines interleukin (IL)-6 and **tumor** necrosis factor (TNF)-.alpha., in the **bone**. Middle ear bone responded rapidly to bacterial challenge, and the reaction depended upon the causative agent. On day 1, IL-6 and TNF-.alpha. transcripts were detected in the bone from all middle ears. After a short period of decreased expression of **osteocalcin**, during which the otitis diagnosis could not be made clin., the levels of bone formation markers increased dramatically. The max. levels of these markers were reached on days 6 and 14 for animals challenged with H. influenzae and pneumococci, resp. Infections induced by pneumococci had a longer duration, and after the initial phase the prodn. of **osteocalcin** and procollagen transcript were significantly higher in the pneumococcus-infected animals. The results indicate that even in an uncomplicated infection, the bone of the bulla reacts to an acute otitis media with a short period of inhibited **osteoblast** activity followed by a longer period of new bone formation. (c) 2001 Academic Press.

L11 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:881423 CAPLUS
DOCUMENT NUMBER: 134:37065
TITLE: Methods and compositions for identifying inhibitors of **osteoclastic** bone reabsorption
INVENTOR(S): Leitman, Dale; Ribeiro, Ralff C. J.; Baxter, John
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000075660	A1	20001214	WO 2000-US15764	20000607

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-138035 P 19990608

AB Methods are provided for screening a test agent for the ability to reduce **osteoclastic** bone reabsorption. In a preferred embodiment, the methods involve screening the agent for the ability to inhibit tumor necrosis factor (TNF-.alpha.) expression through activity at an inhibitory TNF-.alpha.-responsive element (TNF-RE) in the tumor necrosis factor promoter or through activity at a complex formed by an estrogen receptor at TNF-Re.

IT **9001-78-9, Alkaline phosphatase**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(reporter gene; **osteoclastic** bone reabsorption inhibitor screening)

REFERENCE COUNT: 3
REFERENCE(S):
(1) Davis; US 5426177 A 1995 CAPLUS
(2) Ellis; US 5407820 A 1995 CAPLUS
(3) Sledziewski; US 5284746 A 1994 CAPLUS

L11 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:444520 CAPLUS
DOCUMENT NUMBER: 133:308371
TITLE: Biochemical markers and skeletal metastases
AUTHOR(S): Demers, Laurence M.; Costa, Luis; Lipton, Allan
CORPORATE SOURCE: Departments of Medicine and Pathology, The Penn State University College of Medicine, Hershey, PA, 17033-0850, USA
SOURCE: Cancer (N. Y.) (2000), 88(12, Suppl.), 2919-2926
CODEN: CANCAR; ISSN: 0008-543X
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Skeletal metastases are common occurrences in patients with malignancies such as breast and prostate carcinoma, but they are difficult to diagnose nonradiol., and treatment is difficult to follow clin. Recent developments suggest that biochem. markers of bone remodeling, such as the bone collagen breakdown product N-telopeptide and the bone formation marker known as bone specific **alk. phosphatase**, hold great promise as clin. tools for the management of patients with metastatic bone disease. Serum levels of the **bone** formation marker known as **bone** specific **alk. phosphatase** (BAP), along with serum levels of the **bone** collagen breakdown product carboxyterminal telopeptide of **Type I collagen** (**ICTP**) and urine levels of pyridinoline (PYD), **deoxypyridinoline** (DPD), and N-telopeptide (NTx), were measured in a large cohort of patients with newly **diagnosed** or progressive **cancer** of the breast, prostate, lung, and other sites. Bone marker levels were correlated with the presence or absence of bone scan-documented metastases; metastatic disease extension in terms of the no. of skeletal sites involved; and the type of lesion, whether blastic or lytic. Sites examd. included the pelvis, spine, skull, ribs, and long bones. All of the bone markers examd., including BAP and NTx, were abnormally elevated in a high proportion of patients with confirmed metastases to bone. Urine NTx levels and bone specific **alk. phosphatase** were significantly correlated with the no. of skeletal sites involved, and a significant correlation between marker level and extent of skeletal involvement was also obsd. In addn., both markers were higher in patients with a blastic disease presentation than in patients with osteolytic lesions. Biochem. markers of bone resorption and bone formation are abnormally raised in the blood and urine of patients with metastatic bone disease. Markers of bone collagen breakdown, such as N-telopeptide, as well as markers of **osteoblast** function, such as bone specific **alk. phosphatase**, appear to be of use in assessing and managing patients with malignancies that metastasize to bone. In this study, both NTx and BAP showed a significant correlation with both the presence of bone metastases and the extent of skeletal involvement. Biochem. markers of **bone** remodeling can also be used to guide decision making regarding the treatment of **metastatic bone** disease and to **det.** the effectiveness of therapy for patients with **cancer** to **bone** whose broad-based symptoms make it difficult to discern true response to therapy.

IT **83462-55-9, Deoxypyridinoline**
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(biochem. markers and skeletal metastases)

IT **9001-78-9, Alkaline phosphatase**

RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(bone-specific; biochem. markers and skeletal metastases)

L11 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:382576 CAPLUS
DOCUMENT NUMBER: 133:279744
TITLE: Human metastatic prostate PC3 cell lines degrade bone using matrix metalloproteinases
AUTHOR(S): Sanchez-Sweatman, Otto H.; Orr, F. William; Singh, Gurmit
CORPORATE SOURCE: Hamilton Regional Cancer Centre, McMaster University, Hamilton, ON, L8V 5C2, Can.
SOURCE: Invasion Metastasis (2000), Volume Date 1998-1999, 18(5-6), 297-305
CODEN: INVMDJ; ISSN: 0251-1789
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bone metastases are often assocd. with osteolysis and subsequent pathol. fractures. To **det.** if **metastatic** human **cancer** cells can directly degrade non-mineralized and mineralized **bone**, we used prostate PC3 adenocarcinoma cell lines, which were originally established from skeletal **metastases**. We show that PC3 cells and their conditioned medium degraded non-mineralized, osteoid-like radiolabeled extracellular matrixes from human Saos2 and U2OS **osteoblast** -like cells. These cells also directly degraded mineralized bone by inducing 45Ca release from rat fetal calvariae and forming resorption pits on bone slices, an effect increased by transforming growth factor-.beta.1. A role for matrix metalloproteinases in degrdn. was shown by: (1) stimulation by the phorbol ester TPA of PC3-induced matrix degrdn. and release of matrix metalloproteinase activity; (2) abrogation of matrix degrdn. by 1,10-phenanthroline, a metalloproteinase inhibitor, and (3) degrdn. of purified **type I collagen** by PC3 cells and their conditioned medium. We demonstrate that human prostate cancer cells can directly degrade bone-related matrixes and that matrix metalloproteinases have a role in this process.
REFERENCE COUNT: 46
REFERENCE(S):
(1) Aimes, R; J Biol Chem 1995, V270, P5872 CAPLUS
(5) Centrella, M; Endocr Rev 1994, V15, P27 CAPLUS
(7) Cockett, M; Biochem Soc Trans 1994, V22, P55 CAPLUS
(9) Denhardt, D; Ann NY Acad Sci 1994, V732, P65 CAPLUS

(10) Edwards, D; EMBO J 1987, V6, P1899 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:257017 CAPLUS
DOCUMENT NUMBER: 132:263359
TITLE: Biochemical markers of bone metabolism reflect **osteoclastic** and **osteoblastic** activity in multiple myeloma
AUTHOR(S): Abildgaard, N.; Glerup, H.; Rungby, J.; Bendix-Hansen, K.; Kassem, M.; Brixen, K.; Heickendorff, L.; Nielsen, J. L.; Eriksen, E. F.
CORPORATE SOURCE: Department of Haematology, Aarhus University Hospital, Aarhus, DK-8000, Den.
SOURCE: Eur. J. Haematol. (2000), 64(2), 121-129
CODEN: EJHAEC; ISSN: 0902-4441
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To evaluate the use of recently developed assays of bone metab. in multiple myeloma the authors performed a histomorphometric study of bone biopsies in 16 myeloma patients. Furthermore, the authors measured the levels of interleukin(IL)-6, sol. IL-6 receptor (IL-6sR), IL-1.beta., tumor necrosis factor (TNF) .alpha., TNF.beta., and transforming growth factor (TGF) .beta. in marrow plasma aspirated from the biopsy area. The N-**terminal telopeptide** of collagen I (Ntx) in urine showed a strong pos. correlation with the dynamic histomorphometric indexes of bone resorption (r = 0.68-0.72). Slightly weaker correlations were obsd. between the dynamic indexes of bone resorption and the C-**terminal telopeptide** of collagen I (**ICTP**) in serum (r = 0.57-0.62) and **deoxypyridinoline** (Dpyr) in urine (r = 0.54), whereas urinary pyridinoline (Pyr) did not correlate with the histomorphometric findings. Blood serum C-**terminal propeptide** of procollagen I (**PICP**) and serum bone-specific **alk. phosphatase** (bAP) showed significant correlations with the dynamic parameters of bone formation (r = 0.57-0.58), whereas serum **osteocalcin** and serum total AP did not. Highly significant correlations were obsd. between marrow IL-6 and rates of bone resorption and activation frequency (r = 0.76-0.82) and with serum **ICTP** (r = 0.63). Minor, but also significant correlations were obsd. between the resorptive indexes and IL-6sR and IL-1.beta.. These data indicate that measurements of the biochem. markers of bone metab. may be useful in monitoring myeloma bone disease, and might thus be of use for dose titrn. of bisphosphonate therapy.

IT **9001-78-9, Alkaline phosphatase**
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU

(Occurrence)
(**osteoclastic** and **osteoblastic** bone metab. in multiple myeloma detd. by biochem. markers in blood)
IT **83462-55-9**, **Deoxypyridinoline**
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(**osteoclastic** and **osteoblastic** bone metab. in multiple myeloma detd. by biochem. markers in blood and urine)
REFERENCE COUNT: 43
REFERENCE(S): (2) Abildgaard, N; Br J Haematol 1997, V96, P103 CAPLUS
(4) Abildgaard, N; Eur J Haematol 1998, V61, P128 CAPLUS
(9) Behr, W; Clin Chem 1986, V32, P1960 CAPLUS
(10) Berenson, J; N Engl J Med 1996, V334, P488 CAPLUS
(11) Brincker, H; Br J Haematol 1998, V101, P280 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:145122 CAPLUS
DOCUMENT NUMBER: 132:175806
TITLE: Method for **diagnosing bone metastasis** of malignant **tumor**
INVENTOR(S): Ogata, Etsuro; Koizumi, Mitsuru; Takahashi, Shunji
PATENT ASSIGNEE(S): Japan
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000011480	A1	20000302	WO 1999-JP4480	19990820
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9953025	A1	20000314	AU 1999-53025	19990820

PRIORITY APPLN. INFO.: JP 1998-236146 A 19980821
WO 1999-JP4480 W 19990820

AB Therapeutic effects of drugs on bone metastasis and cancer (mammary cancer, prostatic cancer, lung cancer, etc.)-inducing bone metastasis are evaluated by using a marker reflecting the activity of **osteoblasts** and a marker reflecting the effect of **osteoclasts**, including bone **alk. phosphatase**, **osteocalcin**, type-I procollagen peptide fragments, and crossover index.

IT **9001-78-9**, **Alkaline phosphatase**
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(method for **diagnosing bone metastasis** of malignant **tumor** by using **osteoclast** activity markers)

REFERENCE COUNT: 3
REFERENCE(S):
(1) Koizumi, M; CLINICAL CALSIUM 1998, P98
(2) Nakaba, K; Therapeutic Research 1995, V16(12), P212
(3) Takahashi, S; Biotherapy 1997, V11(1), P75

L11 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:447452 CAPLUS
DOCUMENT NUMBER: 132:62470
TITLE: Induction of differentiation into **osteoblasts** and expression of transcription factor Cbfa1 in neoplastic human salivary cancer cell line
AUTHOR(S): Fukui, Keiichi
CORPORATE SOURCE: Sch. Dent., Univ. Tokushima, Tokushima, 770-8504, Japan
SOURCE: Shikoku Shigakkai Zasshi (1999), 12(1), 157-172
CODEN: SSZAED; ISSN: 0914-6091
PUBLISHER: Shikoku Shigakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Neoplastic clonal HSG-AZA3 cells, prepd. by treating neoplastic human salivary intercalated duct cell line HSG with 5-azacytidine, were cultivated in the presence of vitamin D3 analogs. It has been reported that HSG-AZA3 cells differentiate into **osteoblast** -like cell after treated with 22-oxa-1.alpha.,25-dihydroxyvitamin D3 (22-oxa-1.alpha.,25(OH)2D3). In this study, the effects of vitamin D3 analogs (22-oxa-1.alpha.,25(OH)2D3, 1.alpha.,25(OH)2D3, 24,25(OH)2D3, 1.alpha.(OH)D3:10-7) on HSG-AZA3 cells was examd. Consequently, the growth ofHSG-AZA3 cells was significantly suppressed after treated with 22-oxa-1.alpha.,25(OH)2D3 or 1.alpha.,25(OH)2D3, but not with 24,25(OH)2D3 or 1.alpha.(OH)D3. In addn., the no. of mineralized nodule stained by von Kossa was

significantly increased in the cultured cells treated with 22-oxa-1.alpha.,25(OH)2D3. Moreover, Cbfa1 transcriptional factor was detected by RT-PCR only in the cells treated with 22-oxa-1.alpha.,25(OH)2D3. The tumors prodn. and Cbfa1 gene expression in HSG-AZA3 cell-transplanted nude mice treated with vitamin D3 analogs was examd. The growth of tumor in nude mice treated with 22-oxa-1.alpha.,25(OH)2D3, but not 1.alpha.,25(OH)2D3 or 24,25(OH)2D3 or 1.alpha.(OH)D3 was significantly lower than the untreated control. In addn., **bone** formation was found in the 22-oxa-1.alpha.,25 (OH)2D3 treated group, in which the **tumor** cells around **bone** formation expressed **osteocalcin** protein and Cbfa1 mRNA was **detected** by immunohistochem. staining, RT-PCR or in situ hybridization. Moreover, Cbfa1 mRNA was detected in the HSG-AZA3 cell-transplanted nude mice treated with 22-oxa-1.alpha.,25(OH)2D3. These findings indicate that 22-oxa-1.alpha.,25(OH)2D3 induces expression of Cbfa1 mRNA and differentiation of HSG-AZA3 cells into **osteoblasts**

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L11 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER:	1998:474221 CAPLUS
DOCUMENT NUMBER:	129:156628
TITLE:	Induction of differentiation into **osteoblast**-like cell in neoplastic human salivary cancer cell line HSG-AZA3 after treatment with 22-oxa-1.alpha.,25-dihydroxyvitamin D3
AUTHOR(S):	Yoshioka, Naohito
CORPORATE SOURCE:	Sch. Dent., Univ. Tokushima, Tokushima, 770-8504, Japan
SOURCE:	Shikoku Shigakkai Zasshi (1998), 11(1), 47-62 CODEN: SSZAED; ISSN: 0914-6091
PUBLISHER:	Shikoku Shigakkai
DOCUMENT TYPE:	Journal
LANGUAGE:	Japanese

AB Neoplastic clonal HSG-AZA3 cells, with an acinar cell phenotype, which were induced by 5-azacytidine treatment of neoplastic human salivary intercalated duct cell line HSG, were cultivated in the presence of 22-oxa-1.alpha., 25-dihydroxyvitamin D3 (22-oxa-1.alpha.,25(OH)2D3 : 10-7-10-11 M). It was found by immunoblotting or histochem. staining technique that induction of **type I collagen** and enhanced expression of **alk. Phosphatase** activity were obsd. in the treated cell. In addn., human osteopontin or human osteonectin mRNA as well as human bone sialoprotein mRNA were detected by northern blotting or Nested-polymerase chain reaction (PCR) in these cells. Moreover, formation of bone nodule was obsd. in the cultured cells by von Kossa staining and ultrastructural investigation. The tumors

produced by transplantation into nude mice of HSG-AZA3 cells were treated with 22-oxa-1.alpha., 25(OH)2D3 and examd. for the tumor growth, morphol. and expression of genes encoding bone matrix proteins. Consequently, growth of the **tumor** treated with 22-oxa-1.alpha., 25(OH)2D3 was significantly suppressed as compared with the untreated control and it was found that **bone** formation was induced in the treated **tumor**, in which the **tumor** cells around **bone** formation expressed human osteopontin and osteonectin mRNA as could be **detected** by in situ hybridization. In addn., human **bone** sialoprotein mRNA was **detected** by Nested-PCR in the treated **tumors**. The diffusion chambers contg. 107 of HSG-AZA3 cells were maintained in the growth medium contg. 10-7 M 22-oxa-1.alpha., 25(OH)2D3 for 10 days and then was incubated in the peritoneal cavities of nude mice for further 6 wk. Thereafter, the HSG-AZA3 cells in diffusion chamber were obsd. for the expression of **osteoblast**-related genes. As a consequence, formation of calcified bodies as well as expression of human osteopontin and human osteonectin mRNA were obsd. in the treated cells. The above findings indicate that the induction of **osteoblast**-like cells in human salivary cancer cell line HSG-AZA3 occurs in the presence of 22-oxa-1.alpha., 25(OH)2D3.

IT **9001-78-9, Alkaline phosphatase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(induction of differentiation into **osteoblast**-like cell in neoplastic human salivary cancer cell line HSG-AZA3 after treatment with 22-oxa-1.alpha.,25-dihydroxyvitamin D3)

L11 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:107788 CAPLUS
DOCUMENT NUMBER: 128:255742
TITLE: Monitoring of multiple myeloma patients by simultaneously measuring marker substances of bone resorption and formation
AUTHOR(S): Withold, Wolfgang; Arning, Michael; Schwarz, Martin; Wolf, Hans-Heinrich; Schneider, Wolfgang
CORPORATE SOURCE: Institut fur Klinische Chemie und Laboratoriumsdiagnostik, Heinrich-Heine-Universitat, Moorenstrasse 5, Dusseldorf, D-40225, Germany
SOURCE: Clin. Chim. Acta (1998), 269(1), 21-30
CODEN: CCATAR; ISSN: 0009-8981
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fifteen patients (13 males and two females; mean age, 63 yr; age range, 46-84 yr) with multiple myeloma were studied prospectively

(range of follow-up period, 2-6 mo) to elucidate the diagnostic validity of biochem. markers of bone formation (bone **alk. phosphatase** and the C-**terminal propeptide** of type I procollagen) and bone resorption (urinary excretion of pyridinium cross-links) for monitoring these patients. Eleven of 15 patients received melphalan i.v. and prednisone p.o. every 4 wk. All patients were given pamidronate i.v. for inhibition of bone resorption. The mean values of the urinary excretion of pyridinium cross-links were significantly higher in the patients fulfilling the criteria of 'progression' or 'relapse' than in those showing 'response' and those in the 'plateau phase' ($P<0.05$). In contrast, neither bone **alk. phosphatase** nor C-**terminal propeptide** serum values differed significantly between these two groups ($P<0.05$). The concns. of both bone formation markers were significantly lower in the patients than in the samples obtained from apparently healthy persons ($P<0.001$). There was a significant inverse correlation between the no. of pamidronate courses and the serum concns. of bone **alk. phosphatase** ($P<0.05$). A lack of correlation was obsd. between the urinary excretion of pyridinium cross-links and all other lab. parameters measured (serum concns. of total protein, calcium, creatinine and .beta.2-microglobulin). In conclusion, the urinary excretion of pyridinium cross-links might be a useful parameter for monitoring multiple myeloma patients. Decreased values of bone formation markers may be due to a suppressive effect of the bisphosphonate agents administered or reflect the severity of osteolytic lesions which have been described as being assocd. with unbalanced bone remodelling.

IT **9001-78-9**
RL: ANT (Analyte); BOC (Biological occurrence); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(monitoring of human multiple myeloma by simultaneously measuring marker substances of bone resorption and formation)

L11 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:50124 CAPLUS
DOCUMENT NUMBER: 128:126404
TITLE: Biochemical parameters of bone metabolism in bone metastases of solid tumors
AUTHOR(S): Meijer, W. G.; Van Der Veer, E.; Willemse, P. H. B.
CORPORATE SOURCE: Department of Internal Medicine, University Hospital, Groningen, 9700 RB, Neth.
SOURCE: Oncol. Rep. (1998), 5(1), 5-21
CODEN: OCRPEW; ISSN: 1021-335X
PUBLISHER: Oncology Reports
DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 142 refs. The role of biochem. markers of **bone** metab. in the **diagnosis** and monitoring of **bone metastases** in solid **tumors** is reviewed. Emphasis is on the recently developed markers, which may provide a more accurate quantitation of bone metab. In metastatic bone disease, bone formation and resorption become uncoupled processes, leading to predominantly **osteoblastic** or osteolytic metastases. In osteolytic metastases, bone resorption is enhanced without appropriate acceleration of bone formation. In osteolytic **metastases** the resorption markers are indicated for the **detection** of **bone metastases**. Urinary pyridinium cross-links and serum collagen telopeptides are sensitive and specific markers of bone resorption. These markers, can often identify bone metastases before visualization by imaging techniques. When osteolytic lesions are responding to treatment the physiol. coupling between bone resorption and formation is partly restored. An increase in formation markers, bone specific isoenzyme of **alk. phosphatase** (BSAP), **osteocalcin** (OC) and carboxyterminal propeptide of **collagen type I** (**PICP**), will then closely reflect restoration of coupling. In **osteoblastic** metastases, bone formation markers can accurately indicate early and advanced bone involvement. Bone resorption markers are less sensitive in these **osteoblastic** lesions. The collagen telopeptides however, are resorption markers with the ability to **detect** early **bone metastases**. **Osteoblastic** lesions responding to therapy are indicated by declining values of formation as well as resorption markers. The precise role of the recently developed markers of **bone** metab. in early **diagnosis** and monitoring of **bone metastases** needs further evaluation in longitudinal studies. Since the delicate derangements in bone metab. may be obscured in mixed patient groups, these studies should address uniform patient groups with respect to the primary tumor type.

L11 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:734097 CAPLUS

DOCUMENT NUMBER: 128:33060

TITLE: Comparison of Assay of Total and Bone-Specific **Alkaline Phosphatase** in the Assessment of **Osteoblast** Activity in Patients with Metastatic Bone Disease

AUTHOR(S): Piovesan, A.; Berruti, A.; Torta, M.; Cannone, R.; Sperone, P.; Panero, A.; Gorzegno, G.; Termine, A.; Dogliotti, L.; Angeli, A.

CORPORATE SOURCE: Ospedale San Luigi Gonzaga, Oncologia Medica, Clinica Medica, Centro Interdipartimentale per

lo Studio e la Cura delle Osteopatie
Metaboliche, Regione Gonzole 10, Orbassano,
Turin, 10043, Italy
SOURCE: Calcif. Tissue Int. (1997), 61(5), 362-369
CODEN: CTINDZ; ISSN: 0171-967X
PUBLISHER: Springer-Verlag New York Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The evaluation of response of osseous metastases to systemic treatments is often low as a consequence of the different radiol. appearances that make objective assessment not only difficult but sometimes impossible. Radiog. evidence of recalcification, the UICC criterion of response, is often evident for 6 mo and sometimes may be delayed even more. This accounts for lower response rates in bone with respect to other metastatic sites in clin. trials. A transient rise in bone formation indexes may provide an early indication of bone healing and, along with measurement of symptomatic changes, could ameliorate the response evaluation. Among the biochem. markers of bone formation, total **alk. phosphatase** (TALP) is widely employed, but it lacks specificity. Estn. of bone isoenzyme (E-**BALP**) by electrophoretic techniques is time consuming and semiquant. The immunoradiometric assay (I-**BALP**) seems to overcome these limitations. In this study, the authors compared the two methods of bone isoenzyme estn. with each other and with the levels of bone gla protein (BGP) and carboxy-**terminal propeptide** of type I procollagen (**PICP**) in a group of 136 cancer patients with bone metastases stratified as having lytic or mixed and blastic lesions at x-ray, and in 62 cancer patients without apparent bone involvement. The same indexes were also evaluated prospectively in a patient subset submitted to chemotherapy assocd. with pamidronate. The aims of the study were to evaluate whether I-**BALP** is superior to E-**BALP** and whether both methods of bone isoenzyme estn. are more advantageous than TALP, BGP, and **PICP** in the assessment of **osteoblast** activity either in baseline conditions or in response to treatment. In bone metastatic patients with lytic appearances, values above the cut-off limit were obsd. in 32.1, 23.3, 48.9, 32.9, and 14 for, TALP, E-**BALP**, I-**BALP**, **PICP**, and BGP, while the corresponding percentages in those with blastic/mixed appearances were 74.0, 84.8, 76.9, 51.9, and 43.8, resp. In the patients without bone involvement, values within the normal range were 90.2, 98.2, 89.6, 71.7, and 90.2, resp. Levels of TALP, E-**BALP**, and I-**BALP** were reciprocally correlated in the three groups examd. In bone metastatic patients, however, the degree of correlation of the enzymes with **PICP** and BGP was weak. Liver isoenzyme of **alk. phosphatas** (LALP) was found to correlate with E-**BALP**, but not with I-

BALP, in patients with mixed/blastic lesions. Thirty-eight patients were submitted to pamidronate therapy (60 mg every 3 wk, administered 4 times) in assocn. with cytotoxic treatment. **Osteoblastic** markers were detd. before any administration. Serum TALP, E-**BALP**, and I-**BALP** showed a transient rise in 9 cases, a progressive redn. in 12, no change in 2, and a progressive increase in 6. Changes in E-**BALP** and I-**BALP** from baseline were greater than those of TALP. A divergent pattern between TALP and both I-**BALP** and E-**BALP** was found in 9 patients, whereas a divergent temporal profile between the two methods of bone isoenzyme estn. was recorded in only 3 patients. Eight out of 38 cases obtained a partial recalcification of lytic and mixed lesions. Seven of them showed the concomitant early increase in TALP, E-**BALP**, and I-**BALP** followed by a gradual decline (**osteoblastic** flare), whereas 1 patient demonstrated the flare of E-**BALP** and I-**BALP** but not of TALP. No relation was found between response and temporal changes in BGP and **PICP** serum levels. The authors conclude that I-**BALP** is a useful marker for **detecting** excess **osteoblastic** activity in patients who have at imaging "pure" lytic **bone metastases**. In the longitudinal evaluation of patients receiving multiple pamidronate infusions plus chemotherapy, TALP, E-**BALP**, and I-**BALP**, but not BGP and **PICP**, appeared to be useful to identify responders in bone. A slight advantage of measurements of serum bone isoenzyme (by both techniques) over TALP is apparent, but this study fails to demonstrate a clear superiority of I-**BALP** over E-**BALP**.

IT **9001-78-9**
RL: ANT (Analyte); BOC (Biological occurrence); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(comparison of assay of total and bone-specific **alk. phosphatase** in assessment of **osteoblast** activity in humans with metastatic bone disease)

L11 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:568498 CAPLUS
DOCUMENT NUMBER: 127:232776
TITLE: Serum pyridinoline crosslinks as markers of tumor-induced bone resorption
AUTHOR(S): Nemoto, R.; Nakamura, I.; Nishijima, Y.; Shiobara, K.; Shimizu, M.; Takehara, T.; Ohta, T.; Kiyoki, M.
CORPORATE SOURCE: Department of Urology, Tottori Prefectural Central Hospital, Tottori, Japan
SOURCE: Br. J. Urol. (1997), 80(2), 274-280

CODEN: BJURAN; ISSN: 0007-1331
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim was to assess serum pyridinoline (Py) and **deoxypyridinoline** (dPy), using a new high-performance liq. chromatog. (HPLC) method, as a serum marker to **det.** the incidence of **metastatic bone** disease in an animal model and in the monitoring of patients with or without **metastatic bone** disease from prostate **cancer** and renal cell **carcinoma** (RCC). Female C3H/He mice (8-12 wk old) received a s.c. injection of tumor-cell suspensions of serially transplanted MBT tumors. The tumor cells induced osteolysis assocd. with **osteoclast** proliferation and serum samples were evaluated for Py and dPy using HPLC. The growth of the tumor macroscopically and histol., and the extent of bone loss assessed by radiog., were compared with the serum Py and dPy level. In the clin. study, patients with or without bone metastases from RCC (24 patients) or prostate cancer (37 patients) were monitored using the same techniques and the no. and extent of bone metastases compared with serum Py and dPy levels both in these patients and in 84 healthy control subjects. There was a significant correlation between the bone loss evaluated by radiog. and the level of serum Py in the animal model. Patients with bone metastases from RCC had higher values of Py and dPy than patients without known metastatic bone disease. The serum Py level increased in two patients as metastatic bone disease progressed. Similarly, in patients with prostate cancer, the mean level of serum Py and dPy was higher in patients with bone metastasis than in the control group, and also higher than that in patients without metastases. The serum Py and dPy levels could also distinguish patients with metastatic bone disease with and without a lytic component. Measurements of serum Py appear to provide a good index of increased bone resorption induced by exptl. tumors and in patients with bone metastases from RCC and prostate cancer.

IT **83462-55-9, Deoxypyridinoline**
RL: ANT (Analyte); BOC (Biological occurrence); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(serum pyridinoline crosslinks as markers of tumor-induced bone resorption in animal model and in humans with metastases)

L11 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:273302 CAPLUS
DOCUMENT NUMBER: 127:423
TITLE: Emergence of **osteoblast**-like cells in a neoplastic human salivary cancer cell line after treatment with 22-oxa-1.alpha.,25-

dihydroxyvitamin D3

AUTHOR(S): Sato, Mitsunobu; Iga, Hiroki; Yoshioka, Naoto; Fukui, Keiichi; Kawamata, Hitoshi; Yoshida, Hideo; Hirota, Seiichi; Kitamura, Yukihiko

CORPORATE SOURCE: Second Department of Oral and Maxillofacial Surgery, Tokushima University School of Dentistry, 3 Kuramoto-cho, Tokushima, 770, Japan

SOURCE: Cancer Lett. (Shannon, Irel.) (1997), 115(2), 149-160
CODEN: CALEDQ; ISSN: 0304-3835
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A neoplastic clonal cell line, which was prepd. by 5-azacytidine treatment of a neoplastic human salivary intercalated duct cell line, was cultivated in the presence of 22-oxa-1.alpha.,25-dihydroxyvitamin D3 and 3 mM .beta.-glycerophosphate. Major alterations, such as expression of **type 1 collagen** and **alk. phosphatase** as well as of human osteopontin and osteonectin, were obsd. in these cells with a phenotype similar to **osteoblasts**. In addn., formation of bone nodule was obsd. in the cultured cells. The tumors produced by transplantation into nude mice of the clonal cells were treated with 22-oxa-1.alpha.,25-dihydroxyvitamin D3 and examd. for tumor growth and morphol. Consequently, growth of the treated tumor was significantly suppressed. Moreover, it was found that **bone** formation was induced in the treated **tumor**, in which the **tumor** cells around **bone** formation expressed human osteopontin and osteonectin mRNA as could be **detected** by in situ hybridization. The above findings indicate that the emergence of **osteoblast**-like cells in the human salivary cancer cells occurs in the presence of 22-oxa-1.alpha.,25-dihydroxyvitamin D3 and .beta.-glycerophosphate.

IT **9001-78-9**
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(emergence of **osteoblast**-like cells in a neoplastic human salivary cancer cell line after treatment with 22-oxa-1.alpha.,25-dihydroxyvitamin D3)

L11 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:26686 CAPLUS
DOCUMENT NUMBER: 126:141664
TITLE: Bone sialoprotein in serum of patients with malignant bone diseases
AUTHOR(S): Withold, Wolfgang; Armbruster, Franz P.; Karmatschek, Markus; Reinauer, Hans
CORPORATE SOURCE: Inst. Klinische Chemie, Heinrich-Heine-Univ.

Duesseldorf, Duesseldorf, 40225, Germany
SOURCE: Clin. Chem. (Washington, D. C.) (1997), 43(1), 85-91
CODEN: CLCHAU; ISSN: 0009-9147
PUBLISHER: American Association for Clinical Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bone sialoprotein (BS), a protein synthesized by **osteoblasts** and **osteoclasts** and highly modified posttranslationally, constitutes a predominant fraction of the noncollagenous org. matrix in human bone. We report an assessment of serum concns. of BS detd. by RIA in patients with malignant bone diseases. In patients with bone metastases (according to scintigraphic criteria), serum BS concns. were greater than in patients without bone metastases. However, ROC curve anal. revealed that serum BS was inferior to serum bone **alk. phosphatase** in discriminating between patients with and without bone metastases. Patients with bone metastases showed a weak correlation between serum BS concns. and bone formation markers. Only "traditional" markers of bone formation, but not BS, were correlated with urinary **deoxypyridinoline**. Liver and kidney dysfunction had no significant influence on BS values in these patients (as assessed by anal. of variance). In multiple myeloma patients treated with corticosteroids and bisphosphonates, BS concns. were lower than in tumor patients without bone metastases, and the correlation between BS concns. and the no. of bisphosphonate courses applied was significant. In postmenopausal women, serum BS concns. averaged 142% greater than in premenopausal women. Further studies should be done, therefore, to elucidate whether serum BS is able to predict high bone turnover after menopause.

IT **9001-78-9, Alkaline phosphatase**
83462-55-9, Deoxypyridinoline
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(bone sialoprotein in serum of patients with malignant bone diseases)

L11 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:172747 CAPLUS
DOCUMENT NUMBER: 124:255111
TITLE: New and traditional serum markers of **bone** metabolism in the **detection** of skeletal **metastases**
AUTHOR(S): Plebani, M.; Bernardi, D.; Zaninotto, M.; De Paoli, M.; Secchiero, S.; Sciacovelli, L.
CORPORATE SOURCE: Azienda Ospedaliera di Padova, Department Laboratory Medicine, Padua, 35128, Italy
SOURCE: Clin. Biochem. (1996), 29(1), 67-72

CODEN: CLBIAS; ISSN: 0009-9120
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The evaluation of "new" and "traditional" markers of **osteoblastic** and **osteoclastic** activity, in patients with bone metastases. Our series consist of 40 patients with clin., radiol., and scintigraphic evidence of bone metastases, and 40 age-matched healthy subjects. In all samples, traditional markers were evaluated by measuring total **alk. phosphatase** (**ALP**), tartrate-resistant acid phosphatase (TrACP) activity, and **osteocalcin** (BGP) concn. To assess new biochem. bone markers, bone isoenzyme of **alk. phosphatase** (**ALP**-B) activity, carboxyterminal propeptide of type I procollagen (**PICP**), and carboxyterminal telopeptide of **type I collagen** (**ICTP**) concns. were measured. Our finding showed that the best diagnostic efficiency is provided by **ICTP** (0.94) followed by total **ALP** (0.90), **ALP**-B (0.80), and TrACP (0.76). The efficiency of BGP and **PICP** was, instead, very low (0.64 and 0.60, resp.). Our results confirm the utility of the new serum markers such as **ALP**-B and **ICTP** assays in **detecting bone metastases**.

IT **9001-78-9**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**bone** isoenzyme; new and traditional serum markers of **bone** metab. in the **detection** of skeletal **metastases**)

L11 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:112239 CAPLUS
DOCUMENT NUMBER: 124:168891
TITLE: Method for determination of bone **alkaline phosphatase** activity: analytical performance and clinical usefulness in patients with metabolic and malignant bone diseases
AUTHOR(S): Withold, Wolfgang; Schulte, Ulrike; Reinauer, Hans
CORPORATE SOURCE: Inst. Klin. Chem. Laboratoriumsdiagn., Heinrich-Heine-Univ. Duesseldorf, Duesseldorf, 40225, Germany
SOURCE: Clin. Chem. (Washington, D. C.) (1996), 42(2), 210-07
CODEN: CLCHAU; ISSN: 0009-9147
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We report the performance characteristics of an assay for detn. of bone **alk. phosphatase** (**ALP**) activity after immunoadsorption in microplate wells. Between-run imprecision was between 7.1% and 11.2%. The detection limit was 1.0 U/L. Comparisons with an immunoradiometric test for detn. of bone **ALP** mass concns. yielded the following regression equation: y = 3.11 + 1.33x with y, the bone **ALP** activity concn. (U/L) and x, the bone **ALP** mass concn. .mu.g/L (r + = 0.974, n = 103). Using sera from patients with liver diseases and sera from patients with secondary hyperparathyroidism yielded a cross-reactivity of 20% for circulating liver **ALP** (and its membrane-bound isoform). In patients receiving renal transplants, Z-score anal. revealed that after transplantation the increase in bone **ALP** activity is more pronounced than total **ALP** activity. In **tumor** patients, receiver-operating characteristic anal. revealed that **bone ALP** activity shows the same **diagnostic** efficacy as total **ALP** activity in the **detection** of **bone metastases** (as assessed by **bone** scintigraphy). In multiple myeloma patients, suppressed **osteoblast** activity was well detectable by bone **ALP** activity detn.

IT **9001-78-9**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(anal. performance and clin. usefulness of a method for detn. of bone **alk. phosphatase** in patients with metabolic and malignant bone diseases)

L11 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:3507 CAPLUS
DOCUMENT NUMBER: 122:100151
TITLE: Use of Tandem-R Ostase to study skeletal **alkaline phosphatase** in the metastatic spread of cancers of the breast and prostate
AUTHOR(S): Cooper, E. H.; Forbes, M. A.; Darte, C.
CORPORATE SOURCE: Sch. Med., Univ. Leeds, Leeds, UK
SOURCE: Laboratoriumsmedizin (1994), 18(2), 80-1
CODEN: LABOD3; ISSN: 0342-3026
DOCUMENT TYPE: Journal
LANGUAGE: German

AB The suitability of an immunoradiometric assay (Tandem-R Ostase) for skeletal **alk. phosphatase** (I) in metastatic spread of cancers of the breast and prostate was investigated. I is a suitable parameter for **osteoblastic** activity of bone metastases and for efficiency of therapy. The assay studied is a sensitive method for studying of biochem. changes in bones caused by

cancers of breast or prostate.

IT **9001-78-9, Alkaline phosphatase**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(sensitivity and suitability of skeletal **alk. phosphatase** detn. in serum by Tandem-R Ostase for detecting metastatic spread of breast and prostate cancer in humans)

L11 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:321133 CAPLUS
DOCUMENT NUMBER: 120:321133
TITLE: Differential production of interleukin 6 in human osteosarcoma cells and the possible effects on neoplastic bone metabolism
AUTHOR(S): Motoyama, Teiichi; Hotta, Tetsuo; Watanabe, Hidenobu; Kumanishi, Toshiro; Ichikawa, Takao; Sekiguchi, Morimasa
CORPORATE SOURCE: Sch. Med., Niigata Univ., Niigata, 951, Japan
SOURCE: Virchows Arch. B (1993), 63(5), 277-81
CODEN: VAAZA2; ISSN: 0340-6075
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Interleukin 6 (IL-6) exerts well-established effects on cells of the immune system as well as on various other cell types. The authors have investigated the effects of IL-6 produced by human osteosarcoma cells on tumor cells from two clonal human osteosarcoma cell lines, KSU.C3 and NOS-1.C8. The authors were unable to identify any effects of IL-6 such as cell proliferation, **alk. phosphatase** activity, **osteocalcin** prodn., or collagen synthesis on the bone-forming phenotypes. However, the KSU.C3 cell line, which showed a little osteoid and no bone formation and was accompanied by a few **osteoclasts** in the xenografted tumors, produced high levels of IL-6, the prodn. of which was quickly and easily stimulated by various agents. On the other hand, the NOS-1.C8 cell line, which formed abundant osteoid or **bone** and was accompanied by no **osteoclasts** in the xenografted **tumors**, produced no **detectable** levels of IL-6 without stimulation, and the prodn. of IL-6 in response to IL-1.beta. was slower. The authors' data suggest that IL-6 produced by osteosarcoma cells does not play an important role in bone formation, but may mediate **osteoclastic** bone resorption.

L11 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1989:628438 CAPLUS
DOCUMENT NUMBER: 111:228438
TITLE: Histochemical detection of **osteocalcin**

in normal and pathological human bone
AUTHOR(S): Vermeulen, Anton H. M.; Vermeer, Cees; Bosman, Fred T.
CORPORATE SOURCE: Med. Sch., Univ. Limburg, Maastricht, Neth.
SOURCE: J. Histochem. Cytochem. (1989), 37(10), 1503-8
CODEN: JHCYAS; ISSN: 0022-1554
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The immunohistochem. localization of **osteocalcin** was studied in demineralized, paraffin-embedded normal and pathol. human bone. Acid decalcification protocols appeared to be more suitable for **osteocalcin** detection than mild chelating agents. In normal lamellar bone, **osteocalcin** was detected in osteocytes and along the lamellar bone matrix in fine granular deposits. Under pathol. conditions (osteomyelitis, neoplasia), appositional bone showed immunoreactivity in **osteoblasts** and osteocytes but not in the provisory woven bone matrix. Intense immunoreactivity could be seen at the cell borders of **osteoclasts** and the bone margins of Howship lacunae. In primary **bone**-forming **tumors**, **osteocalcin** immunoreactivity was **detected** in **osteoblasts** and their malignant counterparts. On the basis of these results, it is concluded that optimal preservation of **osteocalcin** is obtained through mild acid decalcifiers. **Osteocalcin** is deposited in bone matrix, esp. that of metabolically inactive bone. In neoplasms, **osteocalcin** could be a marker of **osteoblastic** differentiation.

L11 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1973:94097 CAPLUS
DOCUMENT NUMBER: 78:94097
TITLE: Serum **alkaline phosphatase**. Total activity and isoenzyme determinations made by use of the centrifugal fast analyzer
AUTHOR(S): Statland, Bernard E.; Nishi, H. Harold; Young, D. S.
CORPORATE SOURCE: Clin. Pathol. Dep., Natl. Inst. Health, Bethesda, Md., USA
SOURCE: Clin. Chem. (1972), 18(12), 1468-74
CODEN: CLCHAU
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A kinetic method for serum **alkaline phosphatase** (AP) used the centrifugal analyzer to **det.** total enzyme activity and to measure the isoenzymes in **bone**, liver, and the L-phenylalanine-sensitive fraction (intestine, **tumor**, and placenta). Measurements were made at 30.degree. in diethanolamine buffer, with p-nitrophenylphosphate as substrate.

The AP isoenzymes were sepd. and measured by selective chem. inhibition with 10 mmoles L-phenylalanine per 1. and 3.3 moles urea per 1. Analyses were performed on sera of a group of healthy pediatric and young adult volunteers and, in addn., on sera from patients with clin. documented **osteoblastic** disorders and hepatobiliary diseases. The instrumental error contributed an uncertainty of 0.34%. Significant day-to-day variation in results on the same pooled sample were attributed to possible reactivation of the sera after thawing and standing at room temp. during the day. In the group of normal volunteers, the predominant AP isoenzyme found in sera originated from bone. The activities of the liver and intestinal AP fractions were independent of age, whereas bone AP activity was significantly greater in the 4-12 and 13-17 year age group when compared with adults. In patients with **osteoblastic** disorders the bone fraction was the major contributor to the total serum AP level, while in a case of suspected liver disease the liver fraction was the major contributor.

IT **9001-78-9**
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, centrifugal analyzer in)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 12:15:40 ON 21 MAY 2001)
L12 118 S L6
L13 45 DUP REM L12 (73 DUPLICATES REMOVED)

L13 ANSWER 1 OF 45 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-224791 [19] WPIDS
DOC. NO. NON-CPI: N2000-168360
DOC. NO. CPI: C2000-068829
TITLE: Accurate diagnosis of and evaluation of therapeutic efficacy of drugs on bone metastasis and cancer metastasis, using marker to reflect activity of **osteoblasts** and marker reflecting effect on **osteoblasts**.
DERWENT CLASS: B04 S03
INVENTOR(S): KOIZUMI, M; OGATA, E; TAKAHASHI, S
PATENT ASSIGNEE(S): (OGAT-I) OGATA E
COUNTRY COUNT: 87
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000011480	A1	20000302	(200019)*	JA	22

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM

EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC
LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9953025 A 20000314 (200031)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000011480	A1	WO 1999-JP4480	19990820
AU 9953025	A	AU 1999-53025	19990820

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9953025	A	Based on	WO 200011480

PRIORITY APPLN. INFO: JP 1998-236146 19980821
AN 2000-224791 [19] WPIDS
AB WO 200011480 A UPAB: 20000419
NOVELTY - A method for the **diagnosis** of **bone metastasis** of malignant **tumor** is by using a marker to reflect activity of **osteoblasts** and a marker to reflect the effect of **osteoclasts**, which can also be used for drug evaluation.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a marker reflecting activity of the **osteoblasts** which includes
(a) a marker relating to **osteoblast** proliferation period and matrix-formation period as well as to the calcification period; or
(b) a marker relating to the matrix-maturation period and calcification period; and
(2) a method for evaluating the therapeutic efficacy of a drug by using a marker reflecting the activity of **osteoblasts** and a marker to reflect the effect of **osteoclasts**
USE - The method is for the diagnosis of and evaluation of therapeutic efficacy of drugs on bone metastasis and cancer metastasis including those of mammary cancer, prostate cancer and lung cancer.
ADVANTAGE - No stated advantage given in the specification.
Dwg.0/4

L13 ANSWER 2 OF 45 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2000354700 MEDLINE
DOCUMENT NUMBER: 20354700 PubMed ID: 10898335

TITLE: Biochemical markers and skeletal metastases.
AUTHOR: Demers L M; Costa L; Lipton A
CORPORATE SOURCE: Department of Medicine, The Penn State University College of Medicine, Hershey, Pennsylvania 17033-0850, USA.
SOURCE: CANCER, (2000 Jun 15) 88 (12 Suppl) 2919-26. Ref: 40
Journal code: CLZ; 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000810
Last Updated on STN: 20000810
Entered Medline: 20000727

AB BACKGROUND: Skeletal metastases are common occurrences in patients with malignancies such as breast and prostate carcinoma, but they are difficult to diagnose nonradiologically, and treatment is difficult to follow clinically. Recent developments suggest that biochemical markers of bone remodeling, such as the bone collagen breakdown product N-telopeptide and the bone formation marker known as bone specific **alkaline phosphatase**, hold great promise as clinical tools for the management of patients with metastatic bone disease. METHODS: Serum levels of the bone formation marker known as bone specific **alkaline phosphatase** (BAP), along with serum levels of the bone collagen breakdown product carboxyterminal telopeptide of **Type I collagen** (**ICTP**) and urine levels of pyridinoline (PYD), deoxypridinoline (DPD), and N-telopeptide (NTx), were measured in a large cohort of patients with newly diagnosed or progressive cancer of the breast, prostate, lung, and other sites. Bone marker levels were correlated with the presence or absence of bone scan-documented metastases; metastatic disease extension in terms of the number of skeletal sites involved; and the type of lesion, whether blastic or lytic. Sites examined included the pelvis, spine, skull, ribs, and long bones. RESULTS: All of the bone markers examined, including BAP and NTx, were abnormally elevated in a high proportion of patients with confirmed metastases to bone. Urine NTx levels and bone specific **alkaline phosphatase** were significantly correlated with the number of skeletal sites involved, and a significant correlation between marker level and extent of skeletal involvement was also observed. In addition, both markers were higher in patients with a blastic disease presentation than in patients with osteolytic lesions. CONCLUSIONS: Biochemical markers of bone resorption and bone formation are abnormally raised in the blood and urine of patients

with metastatic bone disease. Markers of bone collagen breakdown, such as N-telopeptide, as well as markers of **osteoblast** function, such as bone specific **alkaline phosphatase**, appear to be of use in assessing and managing patients with malignancies that metastasize to bone. In this study, both NTx and BAP showed a significant correlation with both the presence of bone metastases and the extent of skeletal involvement. Biochemical markers of bone remodeling can also be used to guide decision making regarding the treatment of **metastatic bone** disease and to **determine** the effectiveness of therapy for patients with cancer to bone whose broad-based symptoms make it difficult to discern true response to therapy.

L13 ANSWER 3 OF 45 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000241628 EMBASE

TITLE: Treatment of bone diseases with bisphosphonates, excluding osteoporosis.

AUTHOR: Devogelaer J.-P.

CORPORATE SOURCE: Prof. J.-P. Devogelaer, Department of Rheumatology, St-Luc University Hospital, Universite Catholique de Louvain, Hippocrate 10, B-1200 Brussels, Belgium. Devogelaer@ruma.ucl.ac.be

SOURCE: Current Opinion in Rheumatology, (2000) 12/4 (331-335).
ISSN: 1040-8711 CODEN: CORHES

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The main biologic action of bisphosphonates consists of the inhibition of **osteoclastic** bone resorption, and, at least, for the drugs introduced after etidronate, without any significant inhibition of bone mineralization. Bisphosphonates therefore play a major role in conditions that are characterized, at least partly, by an increased bone resorption. Primary and secondary osteoporosis by far constitute the most widespread indications for bisphosphonates, mostly because recent published trials have demonstrated their ability to prevent fractures. Potentially crippling conditions such as symptomatic Paget disease of bone remain a major therapeutic challenge for bisphosphonates, but the prevention of the major complications such as sarcoma has still to be proven. The availability of more potent bisphosphonates, less toxic for bones, has certainly widened the therapeutic interventions to asymptomatic patients, bearing in mind the various potential troublesome complications. Fibrous dysplasia resembles, in certain aspects,

Paget disease; it is therefore not surprising that bisphosphonate therapy has been proposed in this indication. With the aging of world populations, more and more cancers will be **diagnosed** . For those with a **bone metastatic** propensity or malignant hematologic condition, such as multiple myeloma, the most recent generation of more potent bisphosphonates may bring more comfort to crippled patients and even, hopefully, have a direct antitumoral activity, if used synergistically with the armamentarium already available to the clinician. New indications for bisphosphonates include osteogenesis imperfecta both in children and adults. In the future, they might be used in the prevention of erosions in rheumatoid arthritis and of loosening of joint prostheses, as well as possibly in osteoarthritis. Now that the fear of theoretically freezing bone remodeling has been reasonably dismissed, potential uses for bisphosphonates might be considered nearly infinite. (C) 2000 Lippincott Williams and Wilkins, Inc.

L13 ANSWER 4 OF 45 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:36149 BIOSIS
DOCUMENT NUMBER: PREV200100036149
TITLE: Markers in the detection of micrometastasis in leukapheresys of patients with metastatic osteosarcoma.
AUTHOR(S): Valabrega, G. (1); Fagioli, F.; Biasin, E.; Vassallo, E.; Brach, A.; Palmero, A.; Grosso, M.; Comoglio, P. M. (1); Madon, E.; Giordano, S. (1)
CORPORATE SOURCE: (1) Department of Molecular Oncology, Institute for cancer Research and Treatment (IRCC), University of Torino School of Medicine, Torino Italy
SOURCE: Tumori, (July August, 2000) Vol. 86, No. 4 Suppl. 1, pp. 89. print.
Meeting Info.: XV Congress of the Italian Cancer Society Turin, Italy October 05-07, 2000 Italian Cancer Society
. ISSN: 0300-8916.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L13 ANSWER 5 OF 45 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:538898 BIOSIS
DOCUMENT NUMBER: PREV200000538898
TITLE: Serum tartrate-resistant acid phosphatase 5b as a marker of bone resorption in breast cancer.
AUTHOR(S): Halleen, J. (1); Alatalo, S. (1); Janckila, A.; Woitge, H.; Seibel, M.; Vaananen, H. (1)
CORPORATE SOURCE: (1) Department of Anatomy, Institute of Biomedicine, University of Turku, Turku Finland

SOURCE: Tumor Biology, (September, 2000) Vol. 21, No. Supplement 1, pp. 66. print.
Meeting Info.: 28th Meeting of the International Society for Oncodevelopmental Biology and Medicine Munich, Germany September 08-13, 2000
ISSN: 1010-4283.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L13 ANSWER 6 OF 45 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:531162 BIOSIS
DOCUMENT NUMBER: PREV200000531162
TITLE: **Type I collagen** metabolism (**PINP**, **ICTP**) in health and disease.
AUTHOR(S): Risteli, J. (1)
CORPORATE SOURCE: (1) Department of Clinical Chemistry, University of Oulu, Oulu Finland
SOURCE: Tumor Biology, (September, 2000) Vol. 21, No. Supplement 1, pp. 24. print.
Meeting Info.: 28th Meeting of the International Society for Oncodevelopmental Biology and Medicine Munich, Germany September 08-13, 2000
ISSN: 1010-4283.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L13 ANSWER 7 OF 45 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1998408195 MEDLINE
DOCUMENT NUMBER: 98408195 PubMed ID: 9736988
TITLE: [Is skeletal **alkaline phosphatase** a valid staging marker in detection of **osteoblastic** skeletal metastases of prostate carcinoma?].
Ist die Skelettalkalische Phosphatase ein valider Stagingmarker zum Nachweis **osteoblastischer** Skelettmetastasen des Prostatakarzinoms?.
AUTHOR: Wirtz D C; Wolff J M; Ittel T H; Jakse G; Niethard F U
CORPORATE SOURCE: Orthopadische Univ.-Klinik der RWTH Aachen.
SOURCE: ZEITSCHRIFT FUR ORTHOPADIE UND IHRE GRENZGEBIETE, (1998 May-Jun) 136 (3) 255-9.
Journal code: XZ4; 1256465. ISSN: 0044-3220.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981118

AB PURPOSE: For patients with prostate cancer (CaP) the proof of **osteoblastic** bone metastases is decisive regarding the prognosis as well as the therapeutical concept. To evaluate the efficiency of skeletal **alkaline phosphatase** (SAP) as staging marker for bone metastases in prostate cancer, SAP was measured in CaP-patients with and without bone metastases compared with prostate-specific antigen (PSA) as the marker of choice till now. METHOD:73 patients with histological proven, but still untreated CaP were entered into the study. After staging the patients were divided into 3 groups: group I: patients with CaP and bone metastases (n = 21), group II: patients with locally advanced CaP without bone metastases (n = 26), group III: patients with clinically localized CaP without bone metastases (n = 26). Serum concentration for SAP and PSA were determined using radioimmunassay. As reference range we defined serum concentrations for SAP < 19 ng/ml and for PSA < 100 ng/ml. RESULTS:71% of the patients with bone metastases (group I) showed elevated SAP and PSA serum concentrations. In contrast, patients without bone metastases (group II + III) have normal SAP-values (<19 ng/) and in 19% of the cases elevated PSA-values (>100 ng/ml). This resulted in a sensitivity and specificity of 71% and 100% for SAP and 71% and 81% for PSA. The positive predictive value for **osteoblastic** bone metastases was 100% for SAP and 60% for PSA. CONCLUSION: SAP is a useful staging marker in prostate cancer and can contribute for an early **detection** of **osteoblastic bone metastases**.

L13 ANSWER 8 OF 45 JICST-EPlus COPYRIGHT 2001 JST
ACCESSION NUMBER: 980668574 JICST-EPlus
TITLE: Parathyroid Hormone-Related Protein, Bone Metastases and Markers of Tumor-Induced Bone Resorption.
AUTHOR: KONO NORIO; NISHIHARA NORIMITSU
KITAZAWA SOHEI
WAKITA KAZUYUKI
CORPORATE SOURCE: Hyogo Med. Cent. Adult.
Kobe Univ., Sch. of Med.
Yodogawa Christian Hosp.
SOURCE: Nyugan no Rinsho (Japanese Journal of Breast Cancer), (1998) vol. 13, no. 2, pp. 253-259. Journal Code: X0344A (Fig. 2, Tbl. 4, Ref. 32)
ISSN: 0911-2251
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; General Review

LANGUAGE: Japanese
STATUS: New
AB Breast cancer patients frequently developed bone metastases. Parathyroid hormonerelated protein(PTHrP), the main mediator of humoral hypercalcemia of malignancy. Production of PTHrP by breast cancer was associated with development of bone metastases. We have studied the immunohistochemical expression of PTHrP for determine the relationship between primary and metastatic sites from 11 autopsy cases. The 11 cases showed metastases to the lung and the liver, and 9 showed bone metastases at autopsy. At primary sites PTHrP was positive in the 9 cases, while the other 2 cases were negative for PTHrP. Regardless of the intencities of immunohistochemical staining of PTHrP at primary sites, cancer cells at metastatic sites in the liver and the lung were almost all negative for PTHrP. On the other hand, the intensity of the immunochemical staining of PTHrP was strongly positive at all the sites of skeletal metastases. Local secretion of PTHrP in bone increases **osteoclast** activation and producing bone metastases. Metastatic tumor in the bone interfere with normal bone remodeling by **osteoclast** activator such as PTHrP. This metabolic disruption results in increased bone destruction. Bone resorption is currently evaluated by **type I collagen** degeneration products. Serum carboxyterminal telopeptide of **type 1 collagen** (**ICTP**) and pyridinoline(Pyr) as a marker of **bone** resorption were **determined** 29 breast **cancer** with **bone metastases**. **ICTP** and Pyr is useful for evaluation of therapeutic responses of breast cancer with skeletal metastases. (author abst.)

L13 ANSWER 9 OF 45 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999385092 MEDLINE
DOCUMENT NUMBER: 99385092 PubMed ID: 10456133
TITLE: Abnormal serum alkaline and acid phosphatase isoenzymes in female breast cancer patients.
AUTHOR: Agbedana E O; Ebesunun M O
CORPORATE SOURCE: Department of Chemical Pathology, University of Ibadan, Nigeria.
SOURCE: AFRICAN JOURNAL OF MEDICINE AND MEDICAL SCIENCES, (1998 Mar-Jun) 27 (1-2) 65-9.
Journal code: 29G; 7801013. ISSN: 0309-3913.
PUB. COUNTRY: Nigeria
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 19991005

Entered Medline: 19990921

AB Serum total, different isoforms of both alkaline and acid phosphatases, liver function enzymes, calcium, inorganic phosphate, heamatocrit, white blood cells and platelet counts were determined in 50 female patients suffering from breast cancer. The serum total alkaline and total acid phosphatases within the breast cancer group were variable with significant elevation of both enzymes compared with the corresponding control values. The activities of alanine and aspartate transferases were higher than the control values, while the decreases in serum albumin and heamatocrit were statistically significant. In the breast cancer patients, the increases in the activities of both heat and urea labile **alkaline phosphatases** were significant. Similarly, in the patients, the tartrate-labile acid phosphatases activity was significantly elevated while the difference in tartrate resistant activity was not significant. In 9 patients (18%), both total alkaline and acid phosphatases were excessively raised when compared with the control. The increased activities of urea-labile and heat-labile **alkaline phosphatases** as well as tartrate-resistant acid phosphatases are suggestive of increased activities of **osteoclast** and **osteoblasts** associated with **bone metastasis**. A possible **diagnostic** importance of this observation deserves further investigation, using monoclonal antibody techniques.

L13 ANSWER 10 OF 45 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998124619 MEDLINE
DOCUMENT NUMBER: 98124619 PubMed ID: 9458286
TITLE: Biochemical parameters of bone metabolism in bone metastases of solid tumors (review).
AUTHOR: Meijer W G; van der Veer E; Willemse P H
CORPORATE SOURCE: Department of Internal Medicine, University Hospital Groningen, 9700 RB Groningen, The Netherlands.
SOURCE: ONCOLOGY REPORTS, (1998 Jan-Feb) 5 (1) 5-21. Ref: 142
Journal code: C1F; 9422756. ISSN: 1021-335X.
PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980410
Last Updated on STN: 19980410
Entered Medline: 19980402

AB The role of biochemical markers of bone metabolism in the **diagnosis** and monitoring of **bone**

metastases in solid **tumors** is reviewed. Emphasis is on the recently developed markers, which may provide a more accurate quantitation of bone metabolism. In metastatic bone disease, bone formation and resorption become uncoupled processes, leading to predominantly **osteoblastic** or osteolytic metastases. In osteolytic metastases, bone resorption is enhanced without appropriate acceleration of bone formation. In osteolytic metastases the resorption markers are indicated for the **detection** of **bone metastases**. Urinary pyridinium cross-links and serum collagen telopeptides are sensitive and specific markers of bone resorption. These markers, can often identify bone metastases before visualization by imaging techniques. When osteolytic lesions are responding to treatment the physiologic coupling between bone resorption and formation is partly restored. An increase in formation markers, bone specific isoenzyme of **alkaline phosphatase** (BSAP), **osteocalcin** (OC) and carboxyterminal propeptide of **collagen type I** (**PICP**), will then closely reflect restoration of coupling. In **osteoblastic** metastases, bone formation markers can accurately indicate early and advanced bone involvement. Bone resorption markers are less sensitive in these **osteoblastic** lesions. The collagen telopeptides however, are resorption markers with the ability to **detect** early **bone metastases**. **Osteoblastic** lesions responding to therapy are indicated by declining values of formation as well as resorption markers. The precise role of the recently developed markers of bone metabolism in early **diagnosis** and monitoring of **bone metastases** needs further evaluation in longitudinal studies. Since the delicate derangements in bone metabolism may be obscured in mixed patient groups, these studies should address uniform patient groups with respect to the primary tumor type.

L13 ANSWER 11 OF 45 JICST-EPlus COPYRIGHT 2001 JST

ACCESSION NUMBER: 971020182 JICST-EPlus

TITLE: Significance of Carboxyterminal Propeptide of Type I Procollagen(**PICP**) and Carboxyterminal Telopeptide of **Type I Collagen**(**ICTP**) in Patients with Prostate Cancer.

AUTHOR: KOGA HIROFUMI; NAITO SEIJI; HASEGAWA SHUJI; NOMA HIDEYA; YAMAZAKI TAKENARI; NAKAJIMA MICHITAKA; KUMAZAWA JOICHI

CORPORATE SOURCE: Kyushu Univ., Fac. of Med.

SOURCE: Ther Res, (1997) vol. 18, no. 10, pp. 3274-3280. Journal Code: Y0681A (Tbl. 7, Ref. 17) ISSN: 0289-8020

PUB. COUNTRY: Japan

DOCUMENT TYPE: Journal; Article
LANGUAGE: Japanese
STATUS: New

AB Recently bone metabolic markers are expected to play an additional role in the **diagnosis** of **bone metastasis** . Carboxyterminal propeptide of type I procollagen(**PICP**) is regard to be one of osteoplastic markers and carboxyterminal telopeptide of **type I collagen**(**ICTP**) are thought to be one of **osteoblastic** markers. We measured serum level of **PICP** and **ICTP** in 60 patients with prostate cancer and in 44 patients with benign prostate hyperplasia(BPH). Of 60 patients with prostate cancer, 10 were those with newly **diagnosed** prostate **cancer** with **bone metastasis**(group A), 6 were patients with relapsed metastatic bone lesions(group B), 6 were those with relapsed prostate cancer but stable metastatic bone lesions(group C), 12 were those with stable metastatic bone lesion after treatment(group D), 26 were those without bone metastasis(stage B and C prostate cancer)(group E) and 44 were diagnossed clinicaly as BPH(group F). The **PICP** and **ICTP** levels in patients of group A and B were significantly higher than those in patients of group C,D,E and F, respectively. A good correlation was observed between the serum level of **alkaline phosphatase**(**ALP**)(.GAMMA.=0.8956 and 0.6947, respectively). Moreover **PICP** and **ICTP** levels in patients with extent of disease(EOD) grade 3 bone lesions were significantly higher than those in patients with EOD grade 0,1 and 2 bone lesions. Consequtive measurement of these markers during the initial 12 weeks after commencing the hormonal treatment indicated that there was little change in both **PICP** and **ICTP** levels in patients of group E, whereas various types of fluctuation were observed in patients of group A. In conclusion, the serum levels of **PICP** and **ICTP** seem to be a useful, non-invasive markers to assess the metastasis in patient with prostate cancer, but further evaluation is necessary to estimate the effect of treatment. (author abst.)

L13 ANSWER 12 OF 45 CANCERLIT
ACCESSION NUMBER: 1998637984 CANCERLIT
DOCUMENT NUMBER: 98637984
TITLE: Feasibility of a nude rat model of bone metastasis for human breast cancer (Meeting abstract).
AUTHOR: Ishii S; Ikeda T; Enomoto K; Kitajima M M; Nouga K
CORPORATE SOURCE: Kawasaki City Hospital, Japan, 210.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, (1997). Vol. 38, pp. A984.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)

FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199802

AB Breast cancer is most frequently associated with bone metastasis. However, the biology has been poorly understood because of lacking an appropriate animal model of human breast cancer. We have developed a nude rat model of bone metastasis using human breast cancer cell lines (MDA-MB-231, MKL-4). Tumor cells (106 cells) were injected into the thoracic aorta via left carotid artery in female rats aged 8 weeks. Until 8 weeks after the injection, the animals were observed and underwent X ray examination to **detect bone metastasis** every 2 weeks. Serum cross-linked carboxy **terminal telopeptide** of **type I collagen** (ITCP) was also measured by RIA to access bone resorption. At the end, all animals were sacrificed for histological examination. At autopsy, metastatic sites were exclusively bone except one with pulmonary metastasis for MKL-4. The growth properties in each line was different. Bone metastasis generated by MDA-MB-231 was detected in all animals 4 weeks after the injection, predominantly osteolytic. **Osteoclastic** activity was usually enhanced around the **tumor**. **Bone metastasis** by MKL-4 was **detected** 6 weeks later, and both osteolytic and **osteoblastic**. Interestingly, new bone formation was observed into the tumor nests. The mean values of **ICTP** in animals with MDA-MB-231 showed the trend of elevation compared those with MKL-4 at 6 week. Our model will be useful to evaluate repeated serum markers of bone and radiographic examination according to progression of bone metastasis.

L13 ANSWER 13 OF 45 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 97463900 MEDLINE
DOCUMENT NUMBER: 97463900 PubMed ID: 9322601
TITLE: **Osteocalcin** and osteonectin immunoreactivity in the diagnosis of osteosarcoma.
AUTHOR: Fanburg J C; Rosenberg A E; Weaver D L; Leslie K O; Mann K G; Taatjes D J; Tracy R P
CORPORATE SOURCE: Department of Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington, DC 20306-6000, USA.
CONTRACT NUMBER: AG-08777 (NIA)
SOURCE: AMERICAN JOURNAL OF CLINICAL PATHOLOGY, (1997 Oct) 108 (4) 464-73.
Journal code: 3FK; 0370470. ISSN: 0002-9173.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971114

AB Osteosarcomas (OSAs) can be difficult to distinguish histologically from tumors with significantly different biologic potentials and treatment protocols. The correct diagnosis of OSA relies on identification of malignant **osteoblasts** that are capable of producing **neoplastic bone**. To **determine** the use of immunohistochemistry for the diagnosis of OSA, 106 tumors from the Massachusetts General Hospital and the University of Vermont were immunostained with monoclonal antiosteocalcin (OC) and antiosteonectin (ON) antibodies. They included 42 OSAs, 25 non-bone-forming sarcomas, 24 other malignant tumors including lymphomas, carcinomas, and melanomas, and 15 benign bone tumors. Cytoplasmic staining with OC showed 70% sensitivity and 100% specificity, while staining with ON showed 90% sensitivity and 54% specificity for bone-forming tumors, consistently staining cell types other than **osteoblasts**. Of the OSAs, 83% demonstrated matrix staining with one or both antibodies, whereas dense collagen was negative for both antibodies in all tumors. We conclude that tumor cell cytoplasmic staining with monoclonal OC may be helpful in distinguishing OSAs from other malignancies, and staining of extracellular matrix for OC and ON antibodies concurrently may help distinguish bone matrix from dense collagen.

L13 ANSWER 14 OF 45 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 97428014 MEDLINE
DOCUMENT NUMBER: 97428014 PubMed ID: 9284202
TITLE: Serum pyridinoline crosslinks as markers of tumour-induced bone resorption.
AUTHOR: Nemoto R; Nakamura I; Nishijima Y; Shiobara K; Shimizu M; Takehara T; Ohta T; Kiyoki M
CORPORATE SOURCE: Department of Urology, Tottori Prefectural Central Hospital, Japan.
SOURCE: BRITISH JOURNAL OF UROLOGY, (1997 Aug) 80 (2) 274-80. Journal code: B3K; 15740090R. ISSN: 0007-1331.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19971008
Last Updated on STN: 19971008
Entered Medline: 19970922

AB OBJECTIVE: To assess serum pyridinoline (Py) and **deoxypyridinoline** (dPy), using a new high-performance liquid chromatography (HPLC) method, as a serum marker to **determine**

the incidence of **metastatic bone** disease in an animal model and in the monitoring of patients with or without metastatic bone disease from prostate cancer and renal cell carcinoma (RCC). PATIENTS, MATERIALS AND METHODS: Female C3H/He mice (8-12 weeks old) received a subcutaneous injection of tumour-cell suspensions of serially transplanted MBT tumours. The tumour cells induced osteolysis associated with **osteoclast** proliferation and serum samples were evaluated for Py and dPy using HPLC. The growth of the tumour macroscopically and histologically, and the extent of bone loss assessed by radiography, were compared with the serum Py and dPy level. In the clinical study, patients with or without bone metastases from RCC (24 patients) or prostate cancer (37 patients) were monitored using the same techniques and the number and extent of bone metastases compared with serum Py and dPy levels both in these patients and in 84 healthy control subjects. RESULTS: There was a significant correlation between the bone loss evaluated by radiography and the level of serum Py in the animal model. Patients with bone metastases from RCC had higher values of Py and dPy than patients without known metastatic bone disease. The serum Py level increased in two patients as metastatic bone disease progressed. Similarly, in patients with prostate cancer, the mean level of serum Py and dPy was higher in patients with bone metastasis than in the control group, and also higher than that in patients without metastases. The serum Py and dPy levels could also distinguish patients with metastatic bone disease with and without a lytic component. CONCLUSION: Measurements of serum Py appear to provide a good index of increased bone resorption induced by experimental tumours and in patients with bone metastases from RCC and prostate cancer.

L13 ANSWER 15 OF 45 MEDLINE DUPLICATE 7

ACCESSION NUMBER:	97361110 MEDLINE
DOCUMENT NUMBER:	97361110 PubMed ID: 9218004
TITLE:	Serum markers of bone metastases in postmenopausal breast cancer patients treated with formestane.
AUTHOR:	Martinetti A; Bajetta E; Seregni E; Zilembo N; Ferrari L; Noberasco C; Massaron S; Rimassa L; Bombardieri E
CORPORATE SOURCE:	Nuclear Medicine Division, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.
SOURCE:	TUMOUR BIOLOGY, (1997) 18 (4) 197-205. Journal code: TUB; 8409922. ISSN: 0289-5447.
PUB. COUNTRY:	Switzerland
	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	199707
ENTRY DATE:	Entered STN: 19970812

Last Updated on STN: 19980206
Entered Medline: 19970731

AB Bone metabolism marker evaluation is expected to play an auxiliary role in the **diagnosis** and follow-up of **bone metastases** in patients affected by different types of neoplasms. In this study we have evaluated **osteoblastic** and **osteoclastic** markers in 18 patients with **bone metastases** from breast **cancer** at **diagnosis** and for 1 year of follow-up during treatment with the aromatase inhibitor formestane. **Osteoblastic** markers include the carboxy-**terminal propeptide** of type I procollagen, the bone-specific **alkaline phosphatase** and the bone GLA protein. The carboxy-terminal cross-linked telopeptide of **type I collagen** (**ICTP**) was evaluated as a marker of **osteoclastic** activity. The patients were classified into three groups according to clinical response. A good correlation between marker level modifications and clinical evolution of skeletal metastases was observed for all the examined markers. Patients with progressive disease showed increasing levels of all markers, whereas patients in regression showed a reduction compared to the basal levels; patients with stable disease fell in between these two categories. We also found that basal **ICTP** values have prognostic significance: in the stable and progressive disease group they were higher than in the partial response group.

L13 ANSWER 16 OF 45 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 8

ACCESSION NUMBER: 97087361 EMBASE
DOCUMENT NUMBER: 1997087361
TITLE: Significance of bone metabolic markers for **diagnosis** of **bone metastasis**.
AUTHOR: Takahashi S.; Koizumi M.
CORPORATE SOURCE: Dr. S. Takahashi, Cancer Institute Hospital, Japanese Found. for Cancer Research, 1-37-1 Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan
SOURCE: Biotherapy, (1997) 11/1 (75-80).
Refs: 17
ISSN: 0914-2223 CODEN: BITPE
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
033 Orthopedic Surgery
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese

AB The most common procedure for **diagnosis** of **bone metastasis** is **bone** scintigraphy, but it has the

disadvantages of high cost and failure to evaluate therapy response. Recently, several new bone metabolic markers have been developed and applied for **diagnosis** of **bone metastasis** . Most of these markers were reviewed, and bone **alkaline phosphatase** (among bone formation markers) and some collagen cross link metabolites (among bone resorption markers) seem to be most promising. We have investigated the efficacy of several bone metabolic markers: serum carboxy-**terminal telopeptide** of **type 1 collagen** (1CTP) and urinary free **deoxypyridinoline** (fDPD) as bone resorption markers; and serum carboxy-**terminal propeptide** of **type 1 collagen** (P1CP), **osteocalcin** (OC), total **alkaline phosphatase** (**ALP**), and bone **alkaline phosphatase** (BAP) as bone formation markers for **diagnosis** of **bone metastasis** of prostate (**osteoblastic** type), lung (osteolytic type), and breast (mixed type) cancer. In patients with prostate cancer, BAP was most useful for **diagnosis** of **bone metastasis** , but **bone** resorption markers also increased. In follow up, 1CTP was most useful for predicting response to therapy, and more useful than prostate-specific antigen (PSA). In patients with lung cancer, bone resorption markers seemed more useful than bone formation markers for **diagnosis** and follow-up of **bone metastasis**. In patients with breast **cancer**, 1CTP was most effective for **diagnosis** of **bone metastasis** because of no increase in postmenopausal osteoporosis. Combination of resorption and formation markers increased sensitivity. In follow up, bone metabolic markers seemed more useful for predicting therapeutic response of bone metastasis than CEA or CA 15-3. These findings suggest that bone metabolic markers would be useful not only to **detect bone metastases** but also to monitor therapeutic effect, and they could partly substitute for bone scintigraphy.

L13 ANSWER 17 OF 45 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 97095985 MEDLINE
DOCUMENT NUMBER: 97095985 PubMed ID: 8941009
TITLE: Prostate carcinoma staging. Clinical utility of bone **alkaline phosphatase** in addition to prostate specific antigen.
AUTHOR: Morote J; Lorente J A; Encabo G
CORPORATE SOURCE: Department of Urology, Vall d'Hebron University Hospital, Autonoma University of Barcelona, Spain.
SOURCE: CANCER, (1996 Dec 1) 78 (11) 2374-8.
Journal code: CLZ; 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961219

AB BACKGROUND: Biochemical markers of bone disease have been of interest as part of the investigation of prostate carcinoma and the monitoring of skeletal involvement. Bone isoenzyme of the **alkaline phosphatase** (BAP) is an indicator of the metabolism of the **osteoblasts**. An immunoradioanalyses with two monoclonal antibodies in sandwich was developed, allowing an accurate measurement of BAP concentration. The goal of the current study was to compare the clinical performance of BAP and prostate specific antigen (PSA) in patients with untreated prostate carcinoma and to determine whether or not BAP can provide valuable additional information to PSA regarding the degree of skeletal extension in patients with prostate carcinoma. METHODS: BAP and PSA serum concentrations were determined in 140 newly diagnosed prostate carcinoma patients (72 M0 and 68 M1-4). The efficiency of both markers in the prediction of positive bone scans was studied as well as the relationship observed between the concentrations of the two markers and the degree of skeletal involvement. To investigate the potential utility of BAP and PSA in eliminating the need for a bone scan, the negative predictive values for different cutoff points for both markers were calculated. RESULTS: BAP was more efficient than PSA in the prediction of positive bone scans and its level was significantly related to the magnitude of skeletal involvement whereas PSA was only able to distinguish between M0 and M1-4 groups of patients. The highest predictive value for a bone scan result was found for BAP cutoff values between 20 and 30 ng/mL, leading to negative and positive predictive values of 92.6% and 98.2%, respectively. The combination of BAP and PSA both set at a 20 ng/ mL cutoff value yielded a negative predictive value of 100% and the combination of BAP and PSA at 30 ng/mL and 20 ng/mL cutoff values, respectively, increased the positive predictive value to 98.5%. CONCLUSIONS: This study suggests that BAP could be a complementary marker to PSA in the **diagnosis** of **bone** disease in patients with prostate **carcinoma**. Its clinical utility could result in important cost saving implications, eliminating bone scan when PSA ranges from 10 to 20 ng/mL because the predictive negative value of PSA < 20 ng/mL and BAP < 20 ng/mL is 100% in this series. In addition, it could provide useful clinical information regarding the degree of skeletal involvement.

L13 ANSWER 18 OF 45 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:22318 BIOSIS
DOCUMENT NUMBER: PREV199799321521

TITLE: Prostate carcinoma staging: Clinical utility of bone **alkaline phosphatase** in addition to prostate specific antigen.

AUTHOR(S): Morote, Juan (1); Lorente, Jose Antonio; Encabo, Gloria

CORPORATE SOURCE: (1) Hortensias, 17 Premia de Dalt 08338 Spain

SOURCE: Cancer, (1996) Vol. 78, No. 11, pp. 2373-2378. ISSN: 0008-543X.

DOCUMENT TYPE: Article

LANGUAGE: English

AB BACKGROUND. Biochemical markers of bone disease have been of interest as part of the investigation of prostate carcinoma and the monitoring of skeletal involvement. Bone isoenzyme of the **alkaline phosphatase** (BAP) is an indicator of the metabolism of the **osteoblasts**. An immunoradioanalyses with two monoclonal antibodies in sandwich was developed, allowing an accurate measurement of BAP concentration. The goal of the current study was to compare the clinical performance of BAP and prostate specific antigen (PSA) in patients with untreated prostate carcinoma and to determine whether or not BAP can provide valuable additional information to PSA regarding the degree of skeletal extension in patients with prostate carcinoma. METHODS. BAP and PSA serum concentrations were determined in 140 newly diagnosed prostate carcinoma patients (72 M0 and 68 M1-4). The efficiency of both markers in the prediction of positive bone scans was studied as well as the relationship observed between the concentrations of the two markers and the degree of skeletal involvement. To investigate the potential utility of BAP and PSA in eliminating the need for a bone scan, the negative predictive values for different cutoff points for both markers were calculated. RESULTS. BAP was more efficient than PSA in the prediction of positive bone scans and its level was significantly related to the magnitude of skeletal involvement whereas PSA was only able to distinguish between M0 and M1-4 groups of patients. The highest predictive value for a bone scan result was found for BAP cutoff values between 20 and 30 ng/mL, leading to negative and positive predictive values of 92.6% and 98.2%, respectively. The combination of BAP and PSA both set at a 20 ng/mL cutoff value yielded a negative predictive value of 100% and the combination of BAP and PSA at 30 ng/mL and 20 ng/mL cutoff values, respectively, increased the positive predictive value to 98.5%. CONCLUSIONS. This study suggests that BAP could be a complementary marker to PSA in the **diagnosis** of **bone** disease in patients with prostate **carcinoma**. Its clinical utility could result in important cost saving implications, eliminating bone scan when PSA ranges from 10 to 20 ng/mL because the predictive negative value of PSA lt 20 ng/mL and BAP lt 20 ng/mL is 100% in this series. In addition, it could provide useful clinical information regarding the degree of skeletal involvement.

L13 ANSWER 19 OF 45 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 96262145 MEDLINE
DOCUMENT NUMBER: 96262145 PubMed ID: 8664134
TITLE: Biochemical evaluation of bone turnover in cancer patients with bone metastases: relationship with radiograph appearances and disease extension.
AUTHOR: Berruti A; Piovesan A; Torta M; Raucci C A; Gorzegno G; Paccotti P; Dogliotti L; Angeli A
CORPORATE SOURCE: Centro Interdipartimentale per lo Studio delle Osteopatie Metaboliche, Universita di Torino, Ospedale San Luigi Gonzaga, Turin, Italy.
SOURCE: BRITISH JOURNAL OF CANCER, (1996 Jun) 73 (12) 1581-7. Journal code: AV4; 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960819
Last Updated on STN: 19980206
Entered Medline: 19960806

AB Serum bone **alkaline phosphatase** (**BALP**), serum carboxy-**terminal propeptide** of type I procollagen (**PICP**) and serum bone gla protein (BGP) as markers of bone formation, serum carboxy-**terminal telopeptide** of **type I collagen** (**ICTP**) as a marker of collagen resorption and fasting molar ratio of urinary calcium to creatinine (CaCr) and serum parathyroid hormone (PTH) were determined in two groups of cancer patients: 48 with advanced or metastatic disease with negative bone scan and 174 with bone metastases categorised as having lytic, mixed or blastic lesions and with more or fewer than or equal to three sites involved. In patients without apparent bone involvement, bone formation markers were rarely elevated. Conversely, serum **ICTP** was frequently found to be supranormal, showing it to be a non-specific marker for early **detection** of **bone metastases**. As expected, values of **bone** formation markers progressively increased in patients with lytic, mixed and blastic lesions, but **ICTP** levels did not show any differences according to the types of bone appearances, confirming previous reports of elevated **osteoclast** activity also in patients with apparent blastic lesions. Serum PTH increased significantly in patients with lytic compared with patients with mixed and blastic appearances, paralleling the bone formation markers, but CaCr showed the opposite pattern. These data are compatible with calcium entrapment in the bone in patients with increased **osteoblast** activity. This so called 'bone hunger

syndrome' is further confirmed by the finding that in the subgroup of blastic appearances CaCr diminished whereas both **ICTP** and PTH increased according to the extent of tumour load in the bone.

L13 ANSWER 20 OF 45 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 97096192 MEDLINE
DOCUMENT NUMBER: 97096192 PubMed ID: 8941216
TITLE: In vivo implantation of human osteosarcoma cells in nude mice induces bones with human-derived **osteoblasts** and mouse-derived osteocytes.
AUTHOR: Hara A; Ikeda T; Nomura S; Yagita H; Okumura K; Yamauchi Y
CORPORATE SOURCE: Department of Orthopaedic Surgery, Juntendo University, School of Medicine, Tokyo, Japan.
SOURCE: LABORATORY INVESTIGATION, (1996 Nov) 75 (5) 707-17. Journal code: KZ4; 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19980206
Entered Medline: 19961230

AB Two human osteosarcoma cell lines, Hu09 and OST, were suspended in Matrigel (Becton Dickinson Labware, Bedford, Massachusetts) and implanted subcutaneously in the backs of nude mice. To study phenotypic changes of tumor cells and host cells, expression of mRNA for osteopontin (OPN), **osteocalcin** (OC), and osteonectin (ON) was analyzed by in situ hybridization. Bone tissue was formed in the tumors derived from Hu09 cells. OPN mRNA was transcribed predominantly in osteocyte-like cells within the bone, whereas OC mRNA was transcribed in **osteoblast**-like cells that surrounded the bone. ON mRNA was detected in both types of cells. The similarity of the expression pattern of OPN, OC, and ON during osteogenesis of Hu09 cells to that of normal skeletal development suggests that the bone formed in Hu09-implanted mice is the same as normal bone tissue. By DNA-DNA in situ hybridization using a human-specific Alu probe and a mouse-specific m-L1 probe, **osteoblast**-like cells in Hu09 tumorous bone were, however, of human origin, whereas osteocyte-like cells were of mouse origin. In the tumors derived from OST cells, no osteogenesis was observed during the experimental period, and the expression of OPN, OC, and ON was not **detected** in **tumor** cells. An endochondral **bone** formation was not evident when these cells were simply implanted into muscle tissue. An endochondral bone was, however, reactively induced in the host mUscle tissue either

when 1 alpha-hydroxyvitamin D3 and all-transretinoic acid were administered to OST-implanted mice or when Hu09 cells were pretreated with dexamethasone before implantation. Hu09 implantation seems to be a useful tool not only for the study of the differentiation of osteosarcoma cells but also for the investigation of the mechanism of bone formation. This system, using Hu09 and OST, may provide us with a new tool for the isolation of the unidentified factors that induce or inhibit osteogenesis in vivo.

L13 ANSWER 21 OF 45 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 12
ACCESSION NUMBER: 1996:415222 BIOSIS
DOCUMENT NUMBER: PREV199699137578
TITLE: Value of immunohistochemical **detection** of noncollagenous proteins of **bone** for the **diagnosis** of **bone tumours**
.
AUTHOR(S): Serra, Massimo (1); Scotlandi, Katia; Sollazzo, Maria Rosa; Sarti, Manuela; Maurici, Daniela; Benini, Stefania; Picci, Piero; Bertoni, Franco; Baldini, Nicola
CORPORATE SOURCE: (1) Lab. Ricerca Oncol., Ist. Ortopedici Rizzoli, Via di Barbiano 1/10, 40136 Bologna Italy
SOURCE: International Journal of Oncology, (1996) Vol. 9, No. 2, pp. 257-261.
ISSN: 1019-6439.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The expression of osteonectin, osteopontin, bone sialoprotein, and **osteocalcin** was evaluated by immunohistochemistry in 57 cases of osteoid-forming and nonosteoid-forming bone tumours using specific polyclonal antibodies and the avidin-biotin peroxidase complex method. A positive immunostaining was found in all of the osteoidforming tumours (**osteoblastoma** and osteosarcoma), both in the cells and in the extracellular matrix. Among non-osteoidforming tumours, immunoreactivity to noncollagenous proteins was present in the cells but not in the matrix of chondrosarcoma, malignant fibrous histiocytoma, and fibrosarcoma, as well as in the mononuclear component of giant-cell tumours. Contrary to small-cell osteosarcoma, Ewing's sarcoma was always negative for all of the noncollagenous proteins considered. These results suggest that the immunohistochemical evaluation of noncollagenous proteins of bone may be a useful tool for the differential **diagnosis** of **bone neoplasms**, particularly among the heterogeneous group of small round cell tumours.

L13 ANSWER 22 OF 45 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96140763 EMBASE
DOCUMENT NUMBER: 1996140763

TITLE: [Biochemical markers of bone metabolism in metastatic bone disease].
BIOCHEMISCHE MARKER DES KNOCHENSTOFFWECHSELS BEI KNOCHENMETASTASEN.

AUTHOR: Seyfried C.; Seibel M.J.; Woitge H.W.; Pecherstorfer M.; Ziegler R.
CORPORATE SOURCE: Medizinische Klinik I, Universitat Heidelberg, Bergheimer Str. 58,D-69115 Heidelberg, Germany

SOURCE: Klinisches Labor, (1996) 42/4 (257-267).
ISSN: 0941-2131 CODEN: KLLAEA
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry
033 Orthopedic Surgery
LANGUAGE: German
SUMMARY LANGUAGE: German; English

AB Biochemical markers of bone metabolism can be valuable tools for the diagnosis, follow-up control and aftercare of metastatic bone disease. Parameters of bone resorption (hydroxyproline, pyridinium crosslinks, tartrate-resistant acid phosphatase or hypercalciuria) are the most important ones since they reflect the destructive character of invasive bone metastases, either directly or indirectly. Most of the experience has been gained by using urinary hydroxyproline, which allows a relatively precise estimation of the osteclastic activity of bone metastases. Pyridinium crosslinks and urinary calcium excretion seem to be useful markers for the **diagnosis** of **bone metastases** and for therapeutical monitoring. Both are complementary parameters of the metabolism of the collagen matrix and that of the mineralized compartment of bone. On the side of bone formation markers, serum **osteocalcin** (OC) plays an important role in the diagnosis and follow-up and, in the case of multiple myeloma, also as a prognostic indicator. In contrast, no predictive value has been demonstrated so far for any of the other parameters. The clinical importance of bone-specific **alkaline phosphatase** and of the amino-and carboxyterminal type I and III procollagen propeptides remains to be proven in further clinical studies. They might be of advantage in the early diagnosis of medullary metastatic disease, that is to say the stage of the metastasizing process preceding osteolysis.

L13 ANSWER 23 OF 45 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 96173892 MEDLINE
DOCUMENT NUMBER: 96173892 PubMed ID: 8595712
TITLE: Method for determination of bone **alkaline phosphatase** activity: analytical performance

and clinical usefulness in patients with metabolic and malignant bone diseases.

AUTHOR: Withold W; Schulte U; Reinauer H

CORPORATE SOURCE: Institut fur Klinische Chemie und Laboratoriumsdiagnostik, Heinrich-Heine-Universitat Dusseldorf, Germany.

SOURCE: CLINICAL CHEMISTRY, (1996 Feb) 42 (2) 210-7. Journal code: DBZ; 9421549. ISSN: 0009-9147.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199604

ENTRY DATE: Entered STN: 19960424
Last Updated on STN: 19960424
Entered Medline: 19960415

AB We report the performance characteristics of an assay for determination of bone **alkaline phosphatase** (**ALP**) activity after immunoadsorption in microplate wells. Between-run imprecision was between 7.1% and 11.2%. The detection limit was 1.0 U/L. Comparisons with an immunoradiometric test for determination of bone **ALP** mass concentrations yielded the following regression equation: y = 3.11 + 1.33x with y, the bone **ALP** activity concentration (U/L) (and x, the bone **ALP** mass concentration microgram/L) (r +=0.974, n = 103). Using sera from patients with liver diseases and sera from patients with secondary hyperparathyroidism yielded a cross-reactivity of 20% for circulating liver **ALP** (and its membrane-bound isoform). In patients receiving renal transplants, Z-score analysis revealed that after transplantation the increase in bone **ALP** activity is more pronounced than total **ALP** activity. In tumor patients, receiver-operating characteristic analysis revealed that bone **ALP** activity shows the same diagnostic efficacy as total **ALP** activity in the **detection** of **bone metastases** (as assessed by **bone** scintigraphy). In multiple myeloma patients, suppressed **osteoblast** activity was well detectable by bone **ALP** activity determination.

L13 ANSWER 24 OF 45 EMBASE

ACCESSION NUMBER: 96167326 EMBASE

DOCUMENT NUMBER: 1996167326

TITLE: Bone **alkaline phosphatase** (B-**Alp**) as tumour marker in prostatic adenocarcinoma.

AUTHOR: Tizzani A.; Casetta G.; Gamba P.; Gontero P.; Aimo G.

CORPORATE SOURCE: Patologia Urologica, Universita di Torino,Torino, Italy

SOURCE: Acta Urologica Italica, (1996) 10/2 (135-140).
ISSN: 0394-2511 CODEN: AUITE5
COUNTRY: Italy
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The development of bone metastases is a common event in several kinds of tumour. Nearly 50% of patients who present with prostate cancer will develop bone metastases; in these patients, the 2 and 5 years survival percentages are 33 and 15%. The **diagnosis** of **bone metastases** depends on conventional radiology and radionuclide scanning of the uptake of technetium99 labelled biphosphonates. Skeletal scintigraphy is a sensitive but non specific method to **detect bone metastases**; however, it plays an important role in the staging of tumours with a high propensity of developing bone metastases, such as prostate cancer. The use of repeated, expensive bone scan in asymptomatic patients during the follow-up of prostate cancer has become debatable and the question has been raised whether biochemical tests could be a more effective way of **diagnosing bone metastases** and following their response to treatment. The most direct biochemical tests available for investigation of bone metastases are those that reflect alteration of the bone formation and destruction in consequence of the presence of metastatic cells. The urinary excretion of hydroxyproline and **deoxypyridinoline**, a specific collagen crosslink, the serum measurement of the tartrate resistant isoenzyme of acid phosphates, **osteocalcin**, procollagen type III and parathormone related peptide (PTHrp), are the main markers which are under consideration in several studies. Bone metastases in prostate cancer are predominantly **osteoblastic**; several markers are available which reflect bone synthesis but not all of them can be used in clinical practice. Prostate specific antigen (PSA) is now generally accepted as the most useful marker of prostate cancer and has virtually replaced prostate acid phosphates (PAP) in the follow-up of disease. Bone isoenzyme of human alkaline phosphates (B-**ALP**) is thought to be involved in bone formation and skeletal mineralization. Tandem R-Ostase Hybritech is a new immunoradiometric assay for B-**ALP**; preliminary trials have indicated that the assay is valuable for the study of disorders of bone metabolism and now it can be used as a marker of **osteoblastic** activity in patients with tumour with high risk of bone metastases, like prostate and breast. With regard to prostate cancer, the most important trials have studied the interrelationship of B-**ALP** and PSA either in newly diagnosed untreated prostate cancer or in

follow-up of advanced cancer. Many authors, such as Cooper, Curtatolo and their co-workers report their experience with B-**ALP** in prostate cancer which seems to be a good marker of bone metabolism and can be substituted for repeated bone scans especially when the patient is asymptomatic. In our experience, we have determined the B-**ALP** in various prostatic carcinoma stages and its relationship with hormone- and radiotherapy. A total of 82 patients with histologically proven prostatic adenocarcinoma were studied. Pre-treatment levels of B-**ALP** and PSA were measured in 57 stages A, B, C and D1 patients and in 25 stage D2 patients. In addition, we measured B-**ALP** serum levels in 12 patients after radical prostatectomy, with PSA < 0.1 ng/ml and no evidence of progression. These patients underwent neoadjuvant hormone therapy with flutamide and LHRH agonist for 3 months before surgery. Until now our study has confirmed that in the majority of the patients the change of PSA and B-**ALP** showed a similar course, $p < 0.05$, during the response phase and subsequent hormone-resistance. This pattern seems to be independent of the type of therapy. In conclusion, both in our study and in other authors studies', the probable clinical value of B-**ALP** in the management of prostate cancer will be in patients who are at risk of developing bone metastases rather than those with established extensive metastatic disease.

L13 ANSWER 25 OF 45 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 96416927 MEDLINE
DOCUMENT NUMBER: 96416927 PubMed ID: 8819718
TITLE: Serum concentration of pyridinoline cross-linked carboxy-**terminal telopeptide** of **type-I collagen** (**ICTP**) and carboxyterminal propeptide of human type I procollagen (**PICP**) in the **diagnosis** of **bone metastases**.
AUTHOR: Koizumi M; Yamada Y; Takiguchi T; Suzuki C; Akashi T; Nomura E; Yamashita T; Ogata E
CORPORATE SOURCE: Department of Nuclear Medicine, Cancer Institute Hospital, Japan.
SOURCE: KAKU IGAKU [JAPANESE JOURNAL OF NUCLEAR MEDICINE], (1996 Jan) 33 (1) 77-84.
Journal code: KML; 2985202R. ISSN: 0022-7854.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219

Entered Medline: 19961127

AB Recently discovered bone metabolic markers are expected to play an additional role in the **diagnosis** of **bone metastasis**. We measured **bone** metabolic markers, serum pyridinoline cross-linked carboxy-**terminal telopeptide** of **type I collagen** (**ICTP**) and carboxyterminal propeptide of human type I procollagen (**PICP**) in 224 patients with breast cancer (106 with bone metastases), 61 patients with prostatic cancer (30 with bone metastases), 45 patients with lung cancer (17 with bone metastases) and 13 patients with miscellaneous cancers (7 with bone metastasis) and compared the values in the presence and absence of bone metastasis. **ICTP** and **PICP** increased significantly in patients with bone metastases. By the analysis of sensitivity and specificity, the cut-off levels were considered to be 5.0 ng/ml for **ICTP** and 140 ng/ml for **PICP**. In lung cancer (bone metastases are mostly of osteolytic), **ICTP** was excellent marker in **detecting bone metastasis**. In breast **cancer** (**bone metastases** are mostly of mixed type), **ICTP** was good in **detecting bone metastases**. In prostatic **cancer** (**bone metastases** are mostly of **osteoblastic**), **ICTP** and **PICP** were good markers in **detecting** high grade of **bone metastases**. Over all, **ICTP** was more sensitive in the **diagnosis** of **bone metastases** than **PICP**. However, both markers were not effective in **detecting** low grade **bone metastases**. **ICTP** and **PICP** should play a supportive role to imaging modalities in the **diagnosis** of **bone metastases**.

L13 ANSWER 26 OF 45 MEDLINE DUPLICATE 15

ACCESSION NUMBER:	97083253 MEDLINE
DOCUMENT NUMBER:	97083253 PubMed ID: 8929827
TITLE:	New and traditional serum markers of bone metabolism in the detection of skeletal metastases.
AUTHOR:	Plebani M; Bernardi D; Zaninotto M; De Paoli M; Secchiero S; Sciacovelli L
CORPORATE SOURCE:	Department of Laboratory Medicine, Azienda Ospedaliera di Padova, Italy.
SOURCE:	CLINICAL BIOCHEMISTRY, (1996 Feb) 29 (1) 67-72. Journal code: DBV; 0133660. ISSN: 0009-9120.
PUB. COUNTRY:	United States Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	199704

ENTRY DATE: Entered STN: 19970414
Last Updated on STN: 19970414
Entered Medline: 19970403

AB OBJECTIVES: The evaluation of "new" and "traditional" markers of **osteoblastic** and **osteoclastic** activity, in patients with bone metastases. DESIGN AND METHODS: Our series consist of 40 patients with clinical, radiological, and scintigraphic evidence of bone metastases, and 40 age-matched healthy subjects. In all samples, traditional markers were evaluated by measuring total **alkaline phosphatase** (**ALP**), tartrate-resistant acid phosphatase (TrACP) activity, and **osteocalcin** (BGP) concentration. To assess new biochemical bone markers, bone isoenzyme of **alkaline phosphatase** (**ALP**-B) activity, carboxyterminal propeptide of type I procollagen (**PICP**), and carboxyterminal telopeptide of **type I collagen** (**ICTP**) concentrations were measured. RESULTS: Our findings showed that the best diagnostic efficiency is provided by **ICTP** (0.94) followed by total **ALP** (0.90), **ALP**-B (0.80), and TrACP (0.76). The efficiency of BGP and **PICP** was, instead, very low (0.64 and 0.60, respectively). CONCLUSION: Our results confirm the utility of the new serum markers such as **ALP**-B and **ICTP** assays in **detecting bone metastases**.

L13 ANSWER 27 OF 45 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 95252053 MEDLINE
DOCUMENT NUMBER: 95252053 PubMed ID: 7734300
TITLE: **Type I collagen** degradation product (**ICTP**) gives information about the nature of bone metastases and has prognostic value in prostate cancer.
AUTHOR: Kylmala T; Tammela T L; Risteli L; Risteli J; Kontturi M; Elomaa I
CORPORATE SOURCE: Division of Urology, University of Tampere, Finland.
SOURCE: BRITISH JOURNAL OF CANCER, (1995 May) 71 (5) 1061-4. Journal code: AV4; 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950615
Last Updated on STN: 19980206
Entered Medline: 19950606

AB Although osteosclerotic bone metastases are characteristic of prostate cancer, mixed metastases with a lytic component are not uncommon. **Type I collagen** is

synthesised by **osteoblasts** and accounts for about 90% of the organic matrix of bone. We have used new specific immunoassays for **PICP** (carboxy-**terminal propeptide** of type I procollagen) and **ICTP** (cross-linked carboxy-**terminal telopeptide** of **type I collagen**) which allow simultaneous assessment of the synthesis and degradation of **type I collagen** respectively. Forty patients with **bone** metastases due to prostate **cancer** at the time of **diagnosis** were investigated with these methods. Twenty-three of them had sclerotic (S) and 17 had mixed metastases with sclerotic and lytic components (S + L) as assessed by radiographs. The concentrations of **PICP** and **ICTP** in serum as well as the activity of **alkaline phosphatase** (AP) were increased in all patients of the S + L group, who had more aggressive bone disease and a shorter survival than the S group ($P < 0.017$). The **ICTP** level was above the reference range in half of the patients in the S group, whereas the **PICP** and AP levels were elevated in 35%. Of the bone markers, only **ICTP** was of prognostic significance ($P < .05$). We conclude that **ICTP** and **PICP** give information about the type and activity of the skeletal metastases. In addition, **ICTP** predicts prognosis.

L13 ANSWER 28 OF 45 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1995:551129 BIOSIS
DOCUMENT NUMBER: PREV199698565429
TITLE: Bone metabolic markers in bone metastases.
AUTHOR(S): Koizumi, Mitsuru (1); Yamada, Yasuhiko; Takiguchi, Tomohiro; Nomura, Etsuji; Furukawa, Masahiko; Kitahara, Tadashi; Yamashita, Takashi; Maeda, Hiroshi; Takahashi, Shunji; Aiba, Keisuke; Ogata, Etsuro
CORPORATE SOURCE: (1) Dep. Nuclear Med., Cancer Inst. Hosp., Tokyo Japan
SOURCE: Journal of Cancer Research and Clinical Oncology, (1995) Vol. 121, No. 9-10, pp. 542-548. ISSN: 0171-5216.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The efficacy and cost/performance benefit of radionuclide bone scintigraphy in monitoring metastatic bone activity remain controversial. Recently developed bone metabolic markers are expected to play an additional role in the **diagnosis** of **bone metastasis**. We measured **osteoclastic** and **osteoblastic** markers in 267 patients with breast cancer (100 with bone metastasis), 38 patients with prostatic cancer (25 with bone metastasis), 50 patients with lung cancer (12 with

bone metastasis) and 33 patients with miscellaneous cancers (13 with bone metastasis) and compared the values in the presence and absence of bone metastasis. Bone metabolic markers, both **osteoclastic** and **osteoblastic**, increased significantly in patients with bone metastasis. In breast cancer (bone metastasis is mostly of the mixed type), **osteoclastic** markers were good in **detecting bone metastasis**. In prostatic **cancer** (**bone metastasis** is mostly **osteoblastic**), **osteoclastic** and **osteoblastic** markers were equally effective in **detecting bone metastasis**. In lung **cancer** (**bone metastasis** is mostly osteolytic), **osteoclastic** markers were elevated preferentially in bone metastasis. Over all, **osteoclastic** markers were more sensitive in the **diagnosis** of **bone metastasis**, and among **osteoclastic** markers, serum pyridionoline-cross-linked carboxy-**terminal telopeptide** was the most efficient in both specificity (91.0%) and sensitivity (48.6%) for **detecting bone metastasis**.

L13 ANSWER 29 OF 45 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 96158416 MEDLINE
DOCUMENT NUMBER: 96158416 PubMed ID: 8593206
TITLE: **Osteocalcin** expression in primary bone tumors--in situ hybridization and immunohistochemical study.
AUTHOR: Park Y K; Yang M H; Kim Y W; Park H R
CORPORATE SOURCE: Department of Pathology, School of Medicine, Kyung Hee University, Seoul, Korea.
SOURCE: JOURNAL OF KOREAN MEDICAL SCIENCE, (1995 Aug) 10 (4) 263-8.
Journal code: AH4; 8703518. ISSN: 1011-8934.
PUB. COUNTRY: KOREA
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199604
ENTRY DATE: Entered STN: 19960422
Last Updated on STN: 19960422
Entered Medline: 19960411

AB **Osteocalcin** is one of the most abundant noncollagenous proteins found in adult bone. It is a highly conserved gamma-carboxyglutamic acid-containing protein that is believed to be produced exclusively by **osteoblasts**. In this study, intracellular and extracellular localization of **osteocalcin** in osteosarcoma was examined with anti-**osteocalcin** antibody and in situ hybridization using a synthetic

oligonucleotide. Immunohistochemically, **osteoblastic** osteosarcomas were all positive for **osteocalcin**. The chondroblastic osteosarcomas were positive on the neoplastic chondrocytes. The five fibroblastic osteosarcomas out of seven were positive for **osteocalcin** immunostaining over the neoplastic spindle cells. Five cases of **osteoblastic** osteosarcomas out of seven were positive for **osteocalcin** in situ hybridization. Two cases of chondroblastic osteosarcomas and three cases of fibroblastic osteosarcomas were positive for in situ demonstration of **osteocalcin**. The malignant tumor giant cells were positive for **osteocalcin** immunostaining 83%. They were also positive for in situ hybridization. The benign giant cells in five giant cell tumors and five aneurysmal bone cysts were negative for **osteocalcin** immunostaining. The benign giant cells in three chondroblastoma and three Paget's disease were positive for **osteocalcin**. In this study, the **osteocalcin** in situ hybridization and immunostaining has very important meaning for making differential **diagnoses** of, especially giant cell rich **bone** forming **tumors**

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L13 ANSWER 30 OF 45 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95135412 EMBASE
DOCUMENT NUMBER: 1995135412
TITLE: [Bone specific **alkaline phosphatase** : Analytical methods and significance in the diagnosis of bone metabolism].
DIE KNOCHENSPEZIFISCHE **ALKALISCHE PHOSPHATASE**: ANALYTISCHE METHODEN UND WERTIGKEIT IN DER KNOCHENSTOFFWECHSEL-DIAGNOSTIK.
AUTHOR: Haag P.; Seibel M.J.; Werle E.; Ziegler R.
CORPORATE SOURCE: Medizinische Universitatsklinik, Abtl Innere Medizin I, Endokrinologie und Stoffwechsel, Bergheimerstr 58,D-69115 Heidelberg, Germany
SOURCE: Klinisches Labor, (1995) 41/4 (217-227).
ISSN: 0941-2131 CODEN: KLLAEA
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
033 Orthopedic Surgery
LANGUAGE: German
SUMMARY LANGUAGE: German; English
AB **Alkaline phosphatase** (AP) is a widely used clinical parameter in the diagnosis and follow-up of liver and metabolic bone diseases. In subjects without liver disease, total AP can also be a reliable index of the formation of new bone, whereas its clinical significance as a marker of **osteoblast**

activation is limited in the presence of liver disease. This is of particular importance in the case of elderly multimorbid patients, so that selective measurement of bone-specific AP is increasingly preferred under osteologic aspects. Among the various systems available for measuring bone-specific AP, isoenzyme electrophoresis and newer immunoassays are best suited for routine purposes. Electrophoretic separation usually allows the relation of the main fractions to the known AP isoenzymes. In some cases, additional enzyme inactivating or enzyme inhibiting methods may be necessary for a further classification. For quantitative analysis of bone-specific AP, however, immunoradiometric methods rather than densitometric evaluation of the electropherograms should be used. As regards diseases with marked disturbances of bone metabolism (e.g. Paget's disease) determination of bone-specific AP is only indicated in individual cases and under formulation of specific questions, since total AP determination will provide information of equal value in many cases. In contrast, bone-specific AP determination in patients with osteotropically metastasizing malignant tumors may sometimes contribute to the early **detection** of **bone metastases**. In this case of diseases associated with only discrete alterations of bone metabolism, such as osteoporosis and primary hyperparathyroidism, for instance, no dramatic changes in bone-specific AP are to be expected, but a clinical role for this isoenzyme is apparently beginning to emerge, at least for assessing the course of postmenopausal osteoporosis. The diagnostic significance of bone-specific AP has not completely defined as yet, but its determination in various bone diseases can already be regarded as useful addition to other diagnostic procedures, such as osteodensitometry. In comparison to other markers of bone formation, e.g. **osteocalcin** (OC) or **PICP**, the bone-specific AP shows a comparable or partly even better correlation to the stages of development or disease.

L13 ANSWER 31 OF 45 JICST-EPlus COPYRIGHT 2001 JST
ACCESSION NUMBER: 950112940 JICST-EPlus
TITLE: Serum **Osteocalcin** in Patients with Prostate Cancer.
AUTHOR: HASEGAWA SHUJI
KINOSHITA TOKUO
HASUI YOSHIHIRO
KUROZUMI TAKESHI
MORITA ICHIKIRO
KOGA HIROFUMI
ANDO SADAMU
MIYAZAKI NORIYOSHI
HASEGAWA YOSHIHIRO
CORPORATE SOURCE: Kyushu Univ., Fac. of Med.
Saga Med. Sch.

Miyazaki Med. Coll.
Kyushukoseinenkinbyoin
Kokuritsubyoinkyushuiryose
Beppu National Hospital
Kitakyushu Munic. Med. Center
Jpn. Red Cross Soc. Hiroshima Atom. Bomb Hosp.
Mutualaid Assoc. of Public Sch. Teach., Kyushu Cent. Hosp.

SOURCE: Ther Res, (1994) vol. 15, no. 12, pp. 5069-5073.
Journal Code: Y0681A (Fig. 4, Ref. 15)
ISSN: 0289-8020
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Short Communication
LANGUAGE: Japanese
STATUS: New

AB Serum **osteocalcin**, which is produced by **osteoblasts** and released in the blood, is a marker for bone formation and **osteoblastic** activity. We investigated the significance of serum **osteocalcin** as the marker of **bone** metastasis in patients with prostate **cancer**. Serum **osteocalcin** levels were **determined** in a total of 71 patients(prostate cancer without bone metastasis: 9, prostate cancer with bone metastasis: 36, benign prostatic hyperplasia: 26). In patients of prostate cancer with bone metastasis, the relationship between serum **osteocalcin** level and serum level of tumor markers such as prostate specific antigen(PSA), prostatic acid phosphatase(PAP) and **alkaline phosphatase(ALP)** was investigated. Serum **osteocalcin** level was significantly higher in patients of prostate cancer with bone metastasis than those without bone metastasis and patients with benign prostatic hyperplasia. In patients of prostate cancer with bone metastasis, there was a significant relationship between serum **osteocalcin** level and serum **ALP** level, but not serum PSA or PAP level. These results suggest that serum **osteocalcin** can be a useful marker for existence of bone metastasis in patients with prostate cancer. (author abst.)

L13 ANSWER 32 OF 45 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:380281 BIOSIS
DOCUMENT NUMBER: PREV199497393281
TITLE: Efficacy of serum bone **alkaline phosphatase** and urinary excretion of pyridinium cross-links for **detection** of **bone metastases** in **tumor** patients.
AUTHOR(S): Withold, Wolfgang; Khakzad, Hassan; Georgescu, Georghe; Heins, Michael; Vosberg, Henning; Reinauer,

Hans
CORPORATE SOURCE: Dep Clin. Chem. Nuclear Med., Univ. Hosp., Duesseldorf Germany
SOURCE: Clinical Chemistry, (1994) Vol. 40, No. 6, pp. 1011. Meeting Info.: 46th National Meeting of the American Association for Clinical Chemistry, Inc. New Orleans, Louisiana, USA July 17-21, 1994
ISSN: 0009-9147.
DOCUMENT TYPE: Conference
LANGUAGE: English

L13 ANSWER 33 OF 45 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 92303127 MEDLINE
DOCUMENT NUMBER: 92303127 PubMed ID: 1609511
TITLE: Usefulness of a novel monoclonal antibody against human **osteocalcin** in immunohistochemical diagnosis.
AUTHOR: Takada J; Ishii S; Ohta T; Koshiba H; Matsuyama T; Usui M; Yamawaki S; Mori M
CORPORATE SOURCE: Department of Orthopaedic Surgery, Sapporo Medical College, Japan.
SOURCE: VIRCHOWS ARCHIV. A, PATHOLOGICAL ANATOMY AND HISTOPATHOLOGY, (1992) 420 (6) 507-11.
Journal code: XD1; 8302198. ISSN: 0174-7398.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920731
Last Updated on STN: 19920731
Entered Medline: 19920721

AB A novel monoclonal antibody against human **osteocalcin**, recently established in our laboratory, was shown by immunoblotting and immunohistochemistry to react specifically with human **osteoblasts**. In the present study, the antibody was applied to the immunohistochemical **diagnosis** of human **bone tumours**, especially **osteoblastic tumours** . The antibody reacted with all 27 osteosarcomas. No positive reaction was found either in chondrosarcoma, giant cell tumours of bone, soft tissue tumours or epithelial tumours. A positive reaction was found preferentially in the cytoplasm of most of the osteosarcoma cells, but not in the extracellular matrix. Since the antibody reacted with formalin-fixed and paraffin-embedded tissues, it will be a useful tool for routine immunohistochemical diagnosis of **osteoblastic** lesions.

L13 ANSWER 34 OF 45 BIOSIS

ACCESSION NUMBER: 1992:29764 BIOSIS
DOCUMENT NUMBER: BA93:19039
TITLE: CLINICAL EVALUATION ON SERUM **OSTEOCALCIN** IN ADVANCED PROSTATE CANCER PATIENTS.
AUTHOR(S): ABE H; NAKAGAMI Y J; ITO H; IKEDA K; OKA F; NIWA N
CORPORATE SOURCE: DEP. UROL., FIRST HOSP. NIPPON MED. SCH., JAPAN.
SOURCE: ACTA UROL JPN, (1991) 37 (8), 877-880.
CODEN: HIKYAJ. ISSN: 0018-1994.
FILE SEGMENT: BA; OLD
LANGUAGE: Japanese

AB The clinical significance of **osteocalcin** as a marker for advanced prostate cancer was examined. **Osteocalcin** is produced by **osteoblasts** and is also detected in the blood. Its change is a good index of osteomatabolic diseases and especially of the **osteoblastic** activity. In the present study, we examined the serum **osteocalcin** concentration of those patients with urogenital tumor, especially prostate cancer, who had been confirmed for multiple bone-metastasis by clinical examination. These patients comprised an untreated group (15 cases) of patients with prostate cancer presenting confirmed bone-metastasis, and a group of patients without bone-metastasis. The respective serum **osteocalcin** concentrations of these two groups were compared with 51 cases of prostate hypertrophy used as the control group. The findings revealed that the serum **osteocalcin** concentration demonstrated high values in the first group with a tendency toward lowering during treatment. Neither the latter group nor the control group showed high values. On the other hand, false-positive cases (8%), and false-negative cases (20%) were found. In the case of bone-metastasis, these results suggest that measurement of serum **osteocalcin** concentration is useful for clinical periodical observation about the activity of the bone metastatic focus.

L13 ANSWER 35 OF 45 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 92087685 MEDLINE
DOCUMENT NUMBER: 92087685 PubMed ID: 1661059
TITLE: Matrix vesicles in bone tumors. Ultrastructural analysis and their significance in neoplastic bone formation.
AUTHOR: Yoshida H; Miyazaki S; Yumoto T
CORPORATE SOURCE: Department of Pathology, Tottori University School of Medicine, Yonago, Japan.
SOURCE: ACTA PATHOLOGICA JAPONICA, (1991 Aug) 41 (8) 610-7.
Journal code: 1NE; 0372637. ISSN: 0001-6632.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199201

ENTRY DATE: Entered STN: 19920209
Last Updated on STN: 19920209
Entered Medline: 19920117

AB Bone tumors were categorized into **alkaline phosphatase** (ALPase)-positive (2 ossifying fibromas, 1 benign **osteoblastoma** and 16 osteosarcomas) and negative (2 chondromas, 2 chondrosarcomas, 3 non-ossifying fibromas, 2 malignant fibrous histiocytomas and 6 giant cell tumors of bone) groups. Production and distribution of matrix vesicles (MVs) in the tumor tissues were examined to clarify their role in neoplastic bone formation. Four distinct types of MV were isolated primarily in ALPase positive bone tumors: empty, amorphous, crystalline and ruptured MVs. They were formed by budding off from the cytoplasmic projections of the **osteoblastic** tumor cells. The significance of differences in the production rate of MVs between ALPase-positive and negative bone tumors was investigated in view of the predominantly high production of MVs in ALPase-positive bone tumors. Many more mature MVs (crystalline and ruptured) were observed in the **osteoblastic** lesions of osteosarcoma than in the fibroblastic and MFH-like lesions, suggesting an intimate relationship with maturation and differentiation of the **osteoblastic** tumor cells. The above findings indicate that production of MVs is one of the **diagnostic** parameters for **osteoblast**-derived **bone tumors**, as well as ALPase activity, and that vesicle-induced mineralization is a major mineralization mechanism in neoplastic bone formation.

L13 ANSWER 36 OF 45 CANCERLIT
ACCESSION NUMBER: 92678424 CANCERLIT
DOCUMENT NUMBER: 92678424
TITLE: BONE TUMORS.
AUTHOR: Schwartz M K
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY.
SOURCE: Immunol Ser, (1990). Vol. 53, pp. 423-30.
DOCUMENT TYPE: Book; (MONOGRAPH)
General Review; (REVIEW)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199201

AB Bone cancers can be classified into two groups: primary bone cancer and cancer metastatic to bone. Primary bone cancers are derived histogenetically from the **osteoclasts**, whose origin is from hematopoietic cells and from **osteoblasts** that originate from stromal cells. Stromal cells also may differentiate embyrologically into chondroblasts and fibroblasts. Bone cancers also may arise from other hematopoietic and neural cells. **Bone** tumors and the role of **tumor** markers in their **diagnosis** and management are reviewed under the following

headings: benign bone tumors; primary bone tumors (multiple myeloma, Ewing's sarcoma, osteosarcomas, and parathyroid adenomas); and metastatic bone tumors. Except on a limited basis, tumor markers are not primary tools in the **diagnosis** and management of **bone tumors**. When markers such as **alkaline phosphatase** are used, immunochemical methods usually are not used. Several monoclonal antibodies to human osteosarcoma antigens have been described that react positively with osteosarcomas on immunostaining and have been proposed for possible use in imaging and therapy. They have not been used to evaluate circulating antigens. In one study the antibody reacted strongly with 15/17 fresh frozen samples of osteosarcoma as well as with neuroblastoma and rhabdomyosarcoma tissue. An undifferentiated sarcoma, fibrosarcoma, and Ewing's sarcoma tissue reacted weakly. Bone scans and magnetic resonance imaging are at this time the techniques used for the initial diagnosis and for monitoring response to therapy. (30 Refs)

L13 ANSWER 37 OF 45 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 90174768 MEDLINE
DOCUMENT NUMBER: 90174768 PubMed ID: 2407992
TITLE: [Bone tissue and cancer].
Tissu osseux et cancer.
AUTHOR: Rossi J F
CORPORATE SOURCE: Laboratoire des Technologies Nouvelles, Centre Val d'Aurelle-Paul Lamarque, Montpellier, France.
SOURCE: PATHOLOGIE BIOLOGIE, (1990 Jan) 38 (1) 69-79. Ref: 754
Journal code: OSG; 0265365. ISSN: 0369-8114.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199004
ENTRY DATE: Entered STN: 19900601
Last Updated on STN: 19900601
Entered Medline: 19900403

AB Bone remodeling is a constant phenomenon balancing between **osteoblastic** bone formation and **osteoclastic** bone resorption in the neighbourhood of a cellular micro-environment including stromal and hemopoietic cells. Numerous local factors and hormones modulate such a mechanism and act synergistically, usually through the indirect production of **osteoblastic** coupling factors. The majority of the cytokines acting on bone remodeling possess both actions upon activation of mature **osteoclasts** and differentiation of hemopoietic **osteoclast** progenitors.

Components from bone matrix which include non-collagenous bone proteins and other local factors are major products acting on **bone** remodeling. The presence of a **cancer** may **determine** changes in **bone** remodeling, directly through **tumor**-mediated resorption or indirectly through the action of local or systemic factors with or without tumor involvement of bone. Bone remodeling associated with cancer is usually an uncoupled phenomenon with decreased bone formation and increased bone resorption. In B-cell malignancies, abnormal bone remodeling is an early event linked to specific bone involvement. Abnormal **osteoclast** differentiation (micro- or macro-resorption) represents a major difference between myeloma and other B-cell malignancies. Several synergistic factors produced by tumor cells and micro-environment are usually implicated in the pathogenesis of bone lytic lesions, hypercalcemia or histomorphometric bone changes associated with cancers.

L13 ANSWER 38 OF 45 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 89381280 MEDLINE
DOCUMENT NUMBER: 89381280 PubMed ID: 2789247
TITLE: Histochemical detection of **osteocalcin** in normal and pathological human bone.
AUTHOR: Vermeulen A H; Vermeer C; Bosman F T
CORPORATE SOURCE: Department of Pathology, University of Limburg, Medical School, Maastricht, The Netherlands.
SOURCE: JOURNAL OF HISTOCHEMISTRY AND CYTOCHEMISTRY, (1989 Oct) 37 (10) 1503-8.
Journal code: IDZ; 9815334. ISSN: 0022-1554.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198910
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19900309
Entered Medline: 19891020

AB We investigated the immunohistochemical localization of **osteocalcin** in demineralized, paraffin-embedded normal and pathological human bone. Acid decalcification protocols appeared to be more suitable for **osteocalcin** detection than mild chelating agents. In normal lamellar bone, **osteocalcin** was detected in osteocytes and along the lamellar bone matrix in fine granular deposits. Under pathological conditions (osteomyelitis, neoplasia), appositional bone showed immunoreactivity in **osteoblasts** and osteocytes but not in the provisory woven bone matrix. Intense immunoreactivity could be seen at the cell borders of **osteoclasts** and the bone margins of Howship lacunae. In primary **bone**-forming **tumors**,

steocalcin immunoreactivity was **detected** in **steoblasts** and their malignant counterparts. On the basis of these results, we conclude that optimal preservation of **osteocalcin** is obtained through mild acid decalcifiers. **Osteocalcin** is deposited in bone matrix, especially that of metabolically inactive bone. In neoplasms, **osteocalcin** could be a marker of **osteoblastic** differentiation.

L13 ANSWER 39 OF 45 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 88145188 MEDLINE
DOCUMENT NUMBER: 88145188 PubMed ID: 3438611
TITLE: Bone scintigraphy in bone metastases due to prostatic cancer.
AUTHOR: Hidaka H; Ishino Y; Nakayama C; Nakata H; Okamura T
CORPORATE SOURCE: Department of Radiology, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan.
SOURCE: SANGYO IKA DAIGAKU ZASSHI, (1987 Dec 1) 9 (4) 369-77. Journal code: SID; 7909645. ISSN: 0387-821X.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198803
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19880325

AB Findings of bone scintigraphy with 99mTc-MDP were compared with bone radiography and biochemical data including total acid phosphatase (T. ACP), prostatic acid phosphatase (P. ACP), and **alkaline phosphatase** (**ALP**) in 35 patients with histologically proven prostatic **cancer**. **Bone metastases** were **diagnosed** in 20 of 35 cases (57%) by scintigraphy. The common sites of metastases were the pelvic bones, ribs, lumbar and thoracic vertebrae. In vertebrae, metastases were mainly distributed in the lower level. The most frequent radiographic change due to metastases was the **osteoblastic** type. On follow-up studies, there was a relatively good agreement in the results of bone scintigraphy and radiography. However, there was a good number of cases showing discrepancy between either scintigraphy or radiography and laboratory data. Bone scintigraphy seems to be the most contributory in monitoring bone metastases from prostatic cancer.

L13 ANSWER 40 OF 45 JICST-EPlus COPYRIGHT 2001 JST
ACCESSION NUMBER: 870294657 JICST-EPlus
TITLE: Enzyme and immunocytochemical study of osteosarcoma cells in pleural effusion. A case report with a

reference on differential **diagnosis** of **bone tumors**.
AUTHOR: KATAOKA HIDEO; AMANO SHIGERU; SASAHARA MASAKIYO; NISIOKA JUNITI; SUGIYAMA SIGEO
CORPORATE SOURCE: Shigaidai I
SOURCE: Nippon Rinsho Saibo Gakkai Zasshi (Journal of the Japanese Society of Clinical Cytology), (1986) vol. 25, no. 4, pp. 701-705. Journal Code: Y0036A (Fig. 9, Ref. 10)
ISSN: 0387-1193
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: Japanese
STATUS: New

L13 ANSWER 41 OF 45 MEDLINE DUPLICATE 23
ACCESSION NUMBER: 85284567 MEDLINE
DOCUMENT NUMBER: 85284567 PubMed ID: 3875469
TITLE: [**Osteocalcin**, a marker in diseases with elevated bone metabolism].
Osteocalcin, ein Marker bei Erkrankungen mit erhohtem Knochenumsatz.
AUTHOR: Stracke H; Schatz C; Pralle H; Ullmann J; Schatz H
SOURCE: DEUTSCHE MEDIZINISCHE WOCHENSCHRIFT, (1985 Sep 20) 110 (38) 1442-6.
Journal code: ECL; 0006723. ISSN: 0012-0472.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198510
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19851022

AB **Osteocalcin** is synthesized by **osteoblasts** and its concentration in serum is increased when bone metabolism is raised. Radioimmunoassay of serum from 88 healthy adults gave a mean **steocalcin** value for the whole group of 4.11 +/- 1.43 ng/ml. The level rose with age. In seven patients with primary hyperparathyroidism the mean value was markedly raised to 19.37 +/- 9.2 ng/ml, in 23 with metastasizing carcinoma of the breast it was elevated to 6.57 +/- 2.98 ng/ml. Serial measurements in 14 female patients over seven months revealed different changes in **osteocalcin** and **alkaline phosphatase** in some of them. In patients with breast cancer and soft-tissue metastases or without metastases both **osteocalcin** and **alkaline phosphatase** levels were normal. Three of 17 patients with multiple myeloma had increased **osteocalcin**

levels. These results indicate that it is clinically helpful to know **osteocalcin** levels in primary hyperparathyroidism. Determination of **osteocalcin** concentration, in addition to that of **alkaline phosphatase**, can be of value in the postmastectomy management of patients with breast cancer, especially in the early recognition of **bone metastases**. The **diagnostic** value of **osteocalcin** levels in multiple myeloma remains undecided.

L13 ANSWER 42 OF 45 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1984:292380 BIOSIS
DOCUMENT NUMBER: BA78:28860
TITLE: LOBULAR CARCINOMA OF THE BREAST METASTATIC TO BONE WITH UNUSUAL CLINICAL RADIOLOGIC AND PATHOLOGIC FEATURES MIMICKING OSTEO POIKILOSIS.
AUTHOR(S): GHANDUR-MNAYMNEH L; BRODER L E; MNAYMNEH W A
CORPORATE SOURCE: DEP. PATHOL., UNIV. MIAMI, SCH. MED., P.O. BOX 016960, MIAMI, FLA. 33101.
SOURCE: CANCER (PHILA), (1984) 53 (8), 1801-1803. CODEN: CANCAR. ISSN: 0008-543X.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB A 55 yr old woman who underwent a right radical mastectomy for infiltrating lobular carcinoma had multiple diffuse **osteoblastic** bone lesions. Since she was asymptomatic, had no elevation of **alkaline phosphatase**, and the lesions did not take up Tc-pyrophosphate on bone scan, she was thought to have osteopoikilosis. An iliac bone biopsy was performed that showed greatly thickened bony trabeculae with diffuse delicate marrow fibrosis entrapping easily overlooked short strands of small malignant cells. The histologic picture also closely resembled osteopoikilosis. Although infiltrating lobular carcinoma has been recognized as separate from ductal carcinoma in the primary site, its recognition in metastatic foci is still vague. Attention is drawn to its histologic appearance in skeletal metastases so that such lesions will be more recognizable in the future.

L13 ANSWER 43 OF 45 CANCERLIT
ACCESSION NUMBER: 85608803 CANCERLIT
DOCUMENT NUMBER: 85608803
TITLE: SERUM MONITORS OF BONE METASTASIS.
AUTHOR: Khansur T; Yam L T; Tavassoli M
CORPORATE SOURCE: Dept. of Medicine, Univ. of Mississippi Sch. of Medicine, Jackson, MS 39216.
SOURCE: Non-serial, (1983). Bone Metastasis:Monitoring and Treatment. Stoll BA, Parbhoo S, eds. New York, Raven Press.
DOCUMENT TYPE: Book; (MONOGRAPH)

FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 198505
AB Serum markers clinically useful in the assessment of bone metastasis are discussed. These markers include **alkaline phosphatase**, acid phosphatase, products of bone matrix (hydroxyproline, delta-carboxyglutamic acid), products of mineral homeostasis (calcium), products of the feedback loop (calcitonin, parathyroid hormone (PTH)), and products of tumors (carcinoembryonic antigen, alpha-fetoprotein, beta-human chorionic gonadotropin, gross cystic disease fluid protein, paraproteins). While most of the markers discussed lack specificity and cannot discriminate between bone metastasis and other pathological states, the **alkaline phosphatases** have an established role in clinical practice as monitors of metastatic bone disease. They serve, respectively, as indices of **osteoblastic** and **osteoclastic** activities of the bone, and not only reflect the extent of bone metastasis but also indicate the type of bone involvement. Among the other markers discussed, tumor products may be useful for following the course of bone metastasis and the response to therapy in a given pt. They are, however, not useful for the **diagnosis** of **bone metastasis**. (69 Refs)

L13 ANSWER 44 OF 45 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 82066414 EMBASE
DOCUMENT NUMBER: 1982066414
TITLE: Clinical evaluation of carcinoma of the prostate by bone scintigraphy with 99mTC-phosphorous Tc-phosphorous compound.
AUTHOR: Kinoshita M.; Igarashi J.; Nogaki J.; et al.
CORPORATE SOURCE: Dept. Urol., Nihon Univ. Sch. Med., Tokyo, Japan
SOURCE: Japanese Journal of Clinical Urology, (1981) 35/11 (1067-1072).
CODEN: RIHYAC
COUNTRY: Japan
DOCUMENT TYPE: Journal
FILE SEGMENT: 028 Urology and Nephrology
023 Nuclear Medicine
016 Cancer
LANGUAGE: Japanese
SUMMARY LANGUAGE: English
AB Eighty radioisotopic bone scintiscans were carried out on 47 patients with prostatic carcinoma seen over the past 6 years. Abnormal skeletal uptake (positive bone scan) was observed in 30 of the 47 cases (64%), while **osteoblastic** and osteolytic changes of bone X-ray (positive bone survey) were noted in 24 of 47 cases (51%). In 30 cases with positive bone scan, the mean values of ACP and **ALP** were 7.4 K.A. and 524.7 mIU, respectively.

Both ACP and **ALP** showed abnormally high values. Metastases were interpreted by bone scan as well as bone survey at the site of pelvis, lumbar spine and ribs. Bone scan was superior to **bone** survey to **detect** the **metastatic** lesions of cervical spine, sternum, ribs, scapula and thoracic spine. 10 of 12 cases with positive bone scan and bone survey before hormonal therapy showed no significant changes or new lesions after the treatment. However, 2 cases demonstrated a decreased accumulation of radioisotope uptake. One of 9 cases already undergoing hormonal treatment showed absent accumulation of radioisotope and normal bone survey. Abnormal renal images were noted in 21 of 47 cases (45%) at the time of bone scintiscanning. Eight showed faint imaging of bilateral kidney. Faint or absent renal image occurred in the cases of multiple or diffuse **osteoblastic** bone metastases. 13 showed asymmetric renal image; this was observed in the cases of VUR, hydronephrosis and decreased renal function.

L13 ANSWER 45 OF 45 CANCERLIT
ACCESSION NUMBER: 74803210 CANCERLIT
DOCUMENT NUMBER: 74803210
TITLE: PROSTATIC TUMOR ACID PHOSPHATASE PRODUCTION. INFLUENCE OF ANTINEOPLASTIC AGENTS.
AUTHOR: Li M C; Kanwal G; Kim R H
CORPORATE SOURCE: Dept. Intern. Med., Nassau Hosp., Mineola, N.Y.
SOURCE: Urology, (1973). Vol. 1, No. 3, pp. 221-225. ISSN: 0090-4295.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: CATH
LANGUAGE: English
ENTRY MONTH: 197512

AB Mithramycin (MM) and dactinomycin (DC) as well as other antineoplastic agents were admin in varying dosages and at varying times to 8 patient with widespread prostatic **carcinoma** to the **bones** to **determine** the effect of these drugs on serum acid phosphatase (SAP) produced by the tumor. All patient had had bilateral orchiectomy and/or estrogen therapy and the disease was in remission. The dosage of MM was reduced 30-50% and DC, 80%, of the dosages normally recommended for malignant disease. Both MM and DC consistently induced a substantial but brief reduction in SAP which was followed by enzyme rebound shortly after discontinuing the drugs. Similar results were found using methotrexate but not fluorouracil or cytarabine. Pain relief with MM and DC extended beyond SAP suppression but was also brief. A more pronounced and sustained decrease of SAP was found in 3 patient treated with MM (infused 4-6 hr/d x 7 d) + thioTEPA. Intravenous bolus admin was less effective than iv drip over 4-6 hr. The effects of these drugs on **alkaline phosphatase**, fasting

sugar, SGOT and BUN are also presented. Toxicity due to these drugs was mild. A temporary inhibition of the synthesis of SAP by the tumor was achieved following the admin of MM, DC and other antineoplastic agents. Also, **osteoblastic** activity with remission of pain and increased patient mobility was observed in several patient receiving MM + thioTEPA. (10 refs)

(FILE 'MEDLINE' ENTERED AT 12:22:20 ON 21 MAY 2001)

L14 6770 SEA FILE=MEDLINE ABB=ON PLU=ON OSTEOBLASTS/CT
L15 4623 SEA FILE=MEDLINE ABB=ON PLU=ON OSTEOCLASTS/CT
L16 1866 SEA FILE=MEDLINE ABB=ON PLU=ON (L14 OR L15) AND (C4. OR C23.)/CT ← cancer / metastases
L17 45924 SEA FILE=MEDLINE ABB=ON PLU=ON "BONE AND BONES"/CT
L18 274 SEA FILE=MEDLINE ABB=ON PLU=ON L16 AND L17
L19 21 SEA FILE=MEDLINE ABB=ON PLU=ON L18 AND (DIAGNOSIS OR DIAGNOSTIC USE)/CT

L19 ANSWER 1 OF 21 MEDLINE
AN 1999259465 MEDLINE
TI [Clinical imaging of osteo-condensed metastases].
Imagerie clinique des metastases osteocondensantes.
AU Buthiau D; Antoine E C; Lapresle P; Wechsler B; Missenard G; Misset J L; Denarnaud J; Khayat D; Ziza J M
SO REVUE DE MEDECINE INTERNE, (1999 Apr) 20 (4) 353-64. Ref: 62
Journal code: SGJ; 8101383. ISSN: 0248-8663.
AB INTRODUCTION: Due to the occurrence of osteoblastic metastases in the course of various cancers, particularly in the course of prostate cancer, we are faced with diagnosis and follow-up issues different from those associated with lytic metastasis. We therefore analyzed the respective advantages of imaging techniques. CURRENT KNOWLEDGE AND KEY POINTS: Most of the time, osteoblastic metastases are evidenced by standard radiography. Due to its ability to demonstrate metastases localization, extent and signs, CT scan is not only of value when osteoblastic metastases are suspected but also for patient's follow-up. MRI provides further information in regard to both the lesion content and osteoblastic degree. Though MRI must be performed after all other imaging procedures, it is of value for multiplanar study of the whole spine. FUTURE PROSPECTS AND PROJECTS: Studies focusing on either the lesion content and volume or helical CT are in progress and aim at better monitoring follow-up, while the objective of dynamic MRI studies is to better analyze lesion content.

L19 ANSWER 2 OF 21 MEDLINE
AN 1999235684 MEDLINE
TI Stable human calcitonin analogues with high potency on bone together with reduced anorectic and renal actions.
AU Uda K; Kobayashi Y; Hisada T; Orlowski R C; Bastian J W; Arnaud C D;

Wakabayashi K

SO BIOLOGICAL AND PHARMACEUTICAL BULLETIN, (1999 Mar) 22 (3) 244-52. Journal code: BPZ; 9311984. ISSN: 0918-6158.

AB Various derivatives of human calcitonin have been synthesized and their biological characteristics compared with those of existing calcitonins. The acute effects of these analogues in reducing serum calcium levels and suppressing appetite were assessed in rats. A calcitonin analogue, PO-1 (CGNLSTCMLGKLSQELHKLQTYPQTAIGVGAP-NH2), having both the N- and C-terminal ten amino acid sequences those of human calcitonin, and the 12 amino acid central region that of salmon calcitonin, was found to have equal effectiveness with salmon calcitonin and elcatonin for reducing serum calcium levels. Strong hypocalcemic activity was also exhibited by PO-23 ([cyclo-Asp1, Lys7]-[des-Gly2]-[Leu8]-PO-1) and PO-29 ([Asp15, Asn17 , Phe19, His20]-PO-23). PO-23 was prepared by replacing the N-terminal Cys-Cys S-S bond of PO-1 with a ring structure composed of an Asp-Lys peptide bond to enhance physicochemical stability. PO-29 was prepared by modifying the central area of the PO-23 molecule to more closely mimic human calcitonin. When tested in vitro, human calcitonin analogues with a [cyclo-Asp1, Lys7] structure showed biological activities on osteoclast-like cells comparable to those of existing calcitonins (salmon calcitonin and elcatonin) in keeping with their relative potencies for in vivo hypocalcemic action. Acute anorectic activity in rats was strong with salmon calcitonin and elcatonin but relatively reduced with human calcitonin analogues having a [cyclo-Asp1, Lys7] structure. The activities of these analogues on kidney cells were also weaker than that of salmon calcitonin or elcatonin. These results suggest that stable human calcitonin analogues with a [cyclo-Asp1, Lys7] structure suppress bone resorption to a degree similar to that of salmon calcitonin or elcatonin with weaker activities on non-osseous tissues which might be related to adverse reaction.

L19 ANSWER 3 OF 21 MEDLINE

AN 1998247402 MEDLINE

TI Further vascular, bone and autonomic investigations in algodystrophy.

AU Masson C; Audran M; Pascaretti C; Namour A; Saumet J L; Basle M F; Legrand E; Bregeon C; Renier J C

SO ACTA ORTHOPAEDICA BELGICA, (1998 Mar) 64 (1) 77-87. Ref: 29 Journal code: 1G2; 2985165R. ISSN: 0001-6462.

AB Direct clinical observation is the most common means of diagnosing algodystrophy. Further investigations may be helpful to rule out other pathological conditions, such as occult or stress fractures or avascular osteonecrosis and to obtain a better understanding of algodystrophy. Transient vascular hyperpermeability in the affected part is well demonstrated by the clinical findings, the MRI signs, and the three-bone scan features. 99m Technectium EHDP bone scan

provides an evaluation of the vascular abnormalities and of the osteoblastic activity. Dermal microcirculation and its reactions to sympathetic stimuli are investigated by laser doppler fluximetry and videophotometric capillaroscopy. Perhaps the sweat test does unveil what might be specific about algodystrophy. The amount of bone loss in algodystrophy in a few weeks or months is what might be expected over 10 years during the natural history of uncomplicated osteoporosis. An initial fracture is undoubtedly an initiating event in the appearance of algodystrophy, but patients suffering from algodystrophy may still have significant osteoporosis for a long period and hence be at risk for fracture. Densitometry could be an aid to the diagnosis and probably to monitoring treatment as well. The local colonization of fibroblasts following the transient stage of hyperpermeability must be kept in mind to explain the results of joint, bone, muscles or neurological investigations in late algodystrophy.

L19 ANSWER 4 OF 21 MEDLINE
AN 1998054074 MEDLINE
TI The effects of mechanical forces on bones and joints. Experimental study on the rat tail.
AU Pazzaglia U E; Andrini L; Di Nucci A
SO JOURNAL OF BONE AND JOINT SURGERY. BRITISH VOLUME, (1997 Nov) 79 (6) 1024-30.
Journal code: HK7; 0375355. ISSN: 0301-620X.
AB We have used an experimental model employing the bent tail of rats to investigate the effects of mechanical forces on bones and joints. Mechanical strain could be applied to the bones and joints of the tail without direct surgical exposure or the application of pins and wires. The intervertebral disc showed stretched annular lamellae on the convex side, while the annulus fibrosus on the concave side was pinched between the inner corners of the vertebral epiphysis. In young rats with an active growth plate, a transverse fissure appeared at the level of the hypertrophic cell layer or the primary metaphyseal trabecular zone. Metaphyseal and epiphyseal trabeculae on the compressed side were thicker and more dense than those of the distracted part of the vertebra. In growing animals, morphometric analysis of hemiepiphyseal and hemimetaphyseal areas, and the corresponding trabecular bone density, showed significant differences between the compressed and distracted sides. No differences were observed in adult rats. We found no significant differences in osteoclast number between compressed and distracted sides in either age group. Our results provide quantitative evidence of the working of 'Wolff's law'. The differences in trabecular density are examples of remodelling by osteoclasts and osteoblasts; our finding of no significant difference in osteoclast numbers between the hemiepiphyses in the experimental and control groups suggests that the response of living bone to altered strain is

mediated by osteoblasts.

L19 ANSWER 5 OF 21 MEDLINE
AN 95144677 MEDLINE
TI Primary lymphoma of bone. Correlation of magnetic resonance imaging features with cytokine production by tumor cells.
AU Hicks D G; Gokan T; O'Keefe R J; Totterman S M; Fultz P J; Judkins A R; Meyers S P; Rubens D J; Sickel J Z; Rosier R N
SO CANCER, (1995 Feb 15) 75 (4) 973-80.
Journal code: CLZ; 0374236. ISSN: 0008-543X.
AB BACKGROUND. Primary lymphoma of bone is a rare, aggressive neoplasm that can present with a large, soft-tissue mass despite minimal evidence of cortical destruction on plain radiographs. METHODS. High resolution magnetic resonance imaging (MRI) examinations of four patients with primary lymphoma of bone were reviewed retrospectively, and in each case intramedullary tumors demonstrated "penetrating channels" extending through the cortex. The MRI studies were correlated with the histopathologic assessment of the tumor for each patient. Immunohistochemistry was performed for immunophenotyping and for cytokine expression by tumor cells. The cytokines that were investigated were interleukin-1, interleukin-6, and tumor necrosis factor-alpha, molecules known to regulate osteoclastic activity. RESULTS. The linear cortical foci noted on MRI correlated with the histopathologic findings of tumor-associated cutting cones, in proximity to osteoclastic bone resorption. Immunohistochemical stains showed a B-cell phenotype for each tumor and positive immunoreactivity in tumor cells for cytokine mediators that stimulate osteoclastic activation. CONCLUSIONS. These findings indicate that the tumor cells in these cases produce soluble cytokine mediators that may regulate extensive osteoclastic activity. In primary lymphoma of bone, tumor activation of osteoclastic resorption, with production of tumor tunnels through the cortex, may represent one of the mechanisms by which lymphoma escapes the intramedullary space and forms large, soft-tissue masses without extensive cortical destruction.

L19 ANSWER 6 OF 21 MEDLINE
AN 94175097 MEDLINE
TI Case report: hypercalcemia in acute myeloblastic leukemia is caused by osteoclast activation.
AU Kent A B; Weinstein R S
SO AMERICAN JOURNAL OF THE MEDICAL SCIENCES, (1993 Sep) 306 (3) 169-73.
Journal code: 3L2; 0370506. ISSN: 0002-9629.
AB Hypercalcemia in adult T-cell leukemia has been attributed to increased levels of 1,25-dihydroxyvitamin D (1,25(OH)2D), whereas in other types of leukemia, hypercalcemia has been blamed on direct skeletal invasion by malignant cells, ectopic parathyroid hormone (PTH) production or bone-resorbing cytokines. A 51-year-old man was

studied who presented with back pain, circulating myeloblasts, and hypercalcemia. The bone marrow revealed acute myeloblastic leukemia. While the ionized calcium concentration was 8.17 mg/dL (normal, 4.73 to 5.21 mg/dL), the levels of PTH, PTH-related peptide, vitamin D, and thyroxine were normal or subnormal. Bone histomorphometry showed a decreased cortical width with intracortical erosion cavities dissecting into the marrow space. In cancellous bone, the osteoid area, osteoblast perimeter, and tetracycline fluorescence were sparse, whereas the osteoclast perimeter was increased. Persistent marrow fat, the general absence of trabecular narrowing, and the prompt response to calcitonin suggest that the osteoclasts caused the hypercalcemia and lytic lesions, rather than pressure atrophy or osteolysis by leukemic infiltration. Osteoclast activation and subsequent hypercalcemia may have been due to a locally produced cytokine, such as interleukin-1 beta or tumor necrosis factor.

L19 ANSWER 7 OF 21 MEDLINE
AN 93329290 MEDLINE
TI Immunohistochemical localization of bone Gla protein and osteonectin in normal human bone and cartilage tissues, and in osteosarcomas and chondrosarcomas.
AU Chiba H; Matsuyama T
SO NIPPON SEIKEIGEKA GAKKAI ZASSHI. JOURNAL OF THE JAPANESE ORTHOPAEDIC ASSOCIATION, (1993 May) 67 (5) 463-72.
Journal code: ION; 0413716. ISSN: 0021-5325.
AB The immunohistochemical localization of bone Gla protein (BGP) and osteonectin (ON) was investigated in normal human bone and cartilage tissues, and in osteosarcomas and chondrosarcomas with their respective antibodies. In normal bone and heterotopic ossification tissues, BGP and ON were detected in preosteoblasts, osteoblasts and young osteocytes, the reaction of which was strongest in osteoblasts. They were also demonstrated in most osteosarcomas, and their reaction was stronger in osteosarcomas with higher differentiation. These observations suggested that BGP and ON were related to the formation of normal and tumoral osteoid. In contrast, the localization of ON in normal cartilage and chondrosarcoma tissues was markedly different from that of BGP in these tissues. In normal growth cartilage, ON reacted with chondrocytes in hypertrophic and calcifying zone and matrix in calcifying zone, whereas BGP did not react. ON was also demonstrated in the cytoplasm and calcifying portion of most chondrosarcomas. These findings indicated that ON plays an important role in calcification of normal and tumoral cartilage tissues. BGP was detected in poorly differentiated and dedifferentiated chondrosarcomas. Thus, these antibodies are expected to be useful for studying calcification of human bone and cartilage and for the diagnosis of human osteosarcomas and chondrosarcomas.

L19 ANSWER 8 OF 21 MEDLINE
AN 91333377 MEDLINE
TI Skeletal alkaline phosphatase specific activity is an index of the osteoblastic phenotype in subpopulations of the human osteosarcoma cell line SaOS-2.
AU Farley J R; Hall S L; Herring S; Tarbaux N M; Matsuyama T; Wergedal J E
SO METABOLISM: CLINICAL AND EXPERIMENTAL, (1991 Jul) 40 (7) 664-71.
Journal code: MUM; 0375267. ISSN: 0026-0495.
AB During continuous culture with serial passage, the human osteosarcoma cell line SaOS-2 showed a time-dependent decrease in skeletal alkaline phosphatase (ALP) activity. Because this was indicative of heterogeneity, subpopulations of SaOS-2 cells were isolated from replicate low-density cultures. The subpopulations were less heterogeneous and more stable (with respect to ALP) than the parent population. ALP specific activity in the subpopulations ranged from 0.05 to 2.3 U/mg protein, and cytochemical analyses indicated multiple steady-state levels of ALP activity per cell. The amount of ALP activity in SaOS-2 subpopulations was proportional to collagen production ([3H]proline incorporation into collagenase-digestible protein; r = .84, P less than .005), and to parathyroid hormone (PTH)-linked synthesis of cyclic adenosine monophosphate (cAMP) (r = .88, P less than .01). From these data, we inferred that ALP activity in SaOS-2 cells can provide a useful index of the osteoblastic phenotype, and that ALP activity, collagen production, and PTH-linked adenylate cyclase were coordinately regulated in these osteoblast-like osteosarcoma cells (ie, selection of subpopulations for ALP activity coselected for collagen synthesis and PTH-linked synthesis of cAMP). Further comparative studies showed that micromolar fluoride concentrations stimulated cell proliferation ([3H]thymidine incorporation into DNA) in low-ALP SaOS-2 subpopulations, but not in high-ALP cells (P less than .001), and that this differential sensitivity to fluoride was associated with an inverse correlation between fluoride-sensitive acid phosphatase and ALP activities (r = -.91, P less than .001).

L19 ANSWER 9 OF 21 MEDLINE
AN 91004059 MEDLINE
TI Human prostatic cancer cells, PC3, elaborate mitogenic activity which selectively stimulates human bone cells.
AU Perkel V S; Mohan S; Herring S J; Baylink D J; Linkhart T A
SO CANCER RESEARCH, (1990 Nov 1) 50 (21) 6902-7.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
AB Prostatic cancer typically produces osteoblastic metastases which are not attended by marrow fibrosis (i.e., osteoblast but not stromal fibroblast proliferation). In the present study we sought to test the hypothesis that prostatic cancer cells produce factor(s) which act selectively on human osteoblasts. Such a paracrine

mechanism would explain the observed increase in osteoblasts, unaccompanied by an increase in marrow fibroblasts. To test this hypothesis we investigated the mitogenic activity released by the human prostatic tumor cell line, PC3. PC3 cells have been reported previously to produce mitogenic activity for cells that was relatively specific for rat osteoblasts compared to rat fibroblasts. However, the effects of this activity on human cells has not been examined previously. PC3-conditioned medium (CM) (5-50 micrograms CM protein/ml) stimulated human osteoblast proliferation by 200-950% yet did not stimulate human fibroblast proliferation [(3H]thymidine incorporation). PC3 CM also increased cell numbers in human osteoblast but not fibroblast cell cultures. To determine whether the osteoblast-specific mitogenic activity could be attributed to known bone growth factors, specific assays for these growth factors were performed. PC3 CM contained 10 pg insulin-like growth factor (IGF) I, less than 2 pg IGF II, 54 pg basic fibroblast growth factor, and 16 pg transforming growth factor beta/microgram CM protein. None of these growth factors alone or in combination could account for the observed osteoblast-specific PC3 cell-derived mitogenic activity. Furthermore, when 5 micrograms/ml PC3 CM was tested in combination with maximally effective concentrations of either basic fibroblast growth factor, IGF I, IGF II, or transforming growth factor beta, it produced an additive effect suggesting that PC3 CM stimulates osteoblast proliferation by a mechanism independent of these bone mitogens. Biochemical characterization supported the hypothesis that the PC3 cell growth factor was unique from other growth factors. The PC3 growth factor did not bind to heparin and was resistant to acid as well as the reducing agent, dithiothreitol. Sephadex G-75 and fast protein liquid chromatography Mono S cation-exchange chromatography revealed the PC3-derived mitogen to be an Mr 26,000-30,000 basic protein. Therefore, we conclude that PC3 cells release a mitogen which exhibits higher specificity for human osteoblasts than human fibroblasts and is unique from other growth factors tested. Production of this mitogen by human prostatic carcinoma cells could play an etiological role in the intense osteoblast-specific stimulation that occurs at sites of bone metastases.

L19 ANSWER 10 OF 21 MEDLINE
AN 90052733 MEDLINE
TI Estrogen receptors and human bone cells: immunocytochemical studies.
AU Colston K W; King R J; Hayward J; Fraser D I; Horton M A; Stevenson J C; Arnett T R
SO JOURNAL OF BONE AND MINERAL RESEARCH, (1989 Aug) 4 (4) 625-31. Journal code: 130; 8610640. ISSN: 0884-0431.
AB In this immunocytochemical study we have probed a number of human bone cell types and bone preparations for the presence of the estrogen receptor (ER) with two distinct monoclonal antibodies.

Using a well-validated antibody (H222) that recognizes human ER and standard peroxidase-antiperoxidase methodology, we were unable to demonstrate nuclear staining for ER in cultured primary or transformed human bone-derived cells or in fetal bone sections. Attempts to visualize ER in osteosarcoma cell lines (TE85C and HTB96) using a silver enhancement procedure were also unsuccessful. Additionally, we failed to detect immunocytochemical staining for the progesterone receptor (using monoclonal antibody mPR1) in control or estrogen-treated human bone cell cultures. Estrogen and progesterone receptor staining was readily detectable in MCF7 human breast cancer cells. In contrast, with a monoclonal antibody that recognizes a 29 kDa cytoplasmic component (p29) closely related to human ER, we observed specific staining in all the osteoblastlike cells studied. Cytoplasmic staining for this p29 antigen was most intense in primary cultures of human bone-derived cells. It is possible that the relatively abundant but as yet undefined p29 antigen may act as a sensitive marker for the presence of ER in cells at levels below the detection limit of the anti-ER monoclonal antibody. If so, our results are consistent with the presence of ER in osteoblastlike cells at very low concentrations.

L19 ANSWER 11 OF 21 MEDLINE
AN 90041377 MEDLINE
TI Mammary fibroadenoma showing osseous metaplasia: a case report.
AU Nishida Y; Kohno N; Furuya Y; Nakatani T; Kaneko S; Sashikata T; Fujiwara O; Saitoh Y
SO GAN NO RINSHO. JAPANESE JOURNAL OF CANCER CLINICS, (1989 Oct) 35 (12) 1461-5. Ref: 21
Journal code: KIF; 1257753. ISSN: 0021-4949.
AB Discussed is a 33-year-old premenopausal woman who noted a mass in her right breast. On palpation, the tumor was determined as being 3.5 x 2.5 cm in size, well circumscribed, of a firm consistency, and freely movable. Mammography showed a well-defined oval lesion which contained a coarse calcification in the upper external quadrant. An ultrasound study revealed a well-defined oval low echoic lesion with a high echoic portion in the internal echo. The tumor was extirpated and a gross inspection found it to be an ordinary fibroadenoma, 3.2 x 2.5 x 1.5 cm in size. Histologically the lesion was a hyalinized fibroadenoma showing osseous metaplasia. A review of the literature has not revealed cases of a benign breast tumors showing an osseous and/or cartilagenous metaplasia. Notable however is that many reports show mammary osteosarcomas as originating from a fibroadenoma. Thus, this tumor also might have possibly developed into a osteosarcoma.

L19 ANSWER 12 OF 21 MEDLINE
AN 89293480 MEDLINE
TI Heterotopic osteogenesis in porous ceramics induced by marrow cells.

AU Ohgushi H; Goldberg V M; Caplan A I
SO JOURNAL OF ORTHOPAEDIC RESEARCH, (1989) 7 (4) 568-78.
Journal code: JIQ; 8404726. ISSN: 0736-0266.
AB When untreated porous calcium phosphate ceramics were transplanted into subcutaneous (s.c.) or intramuscular (i.m.) sites, fibrovascular tissue grew in the pore region without evidence of bone formation. However, when these same ceramics were combined with syngeneic marrow cells, osteogenesis was observed inside the pore region of the implanted ceramic. The osteogenesis began on the surface of the pore region at approximately 3 weeks postimplantation by a process of intramembranous bone formation, with the de novo bone tissue observed directly interfacing with the ceramic surface. Infrequently, small isolated areas showed cartilage formation with no noticeable endochondral ossification. At 4 weeks postimplantation of the ceramic with marrow cells, the osteogenesis in the ceramic accompanied an observed increase in compressive strength, rigidity, and energy absorption of the ceramic. These results suggest that a combination of porous ceramics and marrow cells may be useful for clinical problems requiring osseous reconstruction.

L19 ANSWER 13 OF 21 MEDLINE
AN 89080904 MEDLINE
TI Immunohistochemical characterization of osteoclasts and osteoclast-like cells with monoclonal antibody MB1 on paraffin-embedded tissues.
AU Chilosi M; Gilioli E; Lestani M; Menestrina F; Fiore-Donati L
SO JOURNAL OF PATHOLOGY, (1988 Nov) 156 (3) 251-4.
Journal code: JLB; 0204634. ISSN: 0022-3417.
AB In this study we provide evidence that MB1, a newly developed monoclonal antibody which reacts with B lymphocytes and a proportion of T cells and monocytes, can be successfully used for the direct immunohistochemical identification of osteoclasts on paraffin-embedded surgical specimens. The antigen(s) recognized by MB1 is present at high density in the cytoplasm of osteoclasts of fetal bone and in the multinucleated cells of human giant cell tumour of bone (osteoclastoma), but is weakly expressed or absent in the giant cells of granulomas. MB1 is thus proposed as a new immunohistochemical marker for osteoclasts on paraffin-embedded material.

L19 ANSWER 14 OF 21 MEDLINE
AN 83087927 MEDLINE
TI [Bone tissue changes after radiation therapy and in acute radiation trauma].
Izmeneniia kostnoi tkani posle luchevoi terapii i pri ostroi radiatsionnoi travme.
AU Krylov V M
SO MEDITSINSKAIA RADIOLOGIIA, (1982 Nov) 27 (11) 80-9. Ref: 130

Journal code: MBI; 2984767R. ISSN: 0025-8334.

L19 ANSWER 15 OF 21 MEDLINE
AN 83062040 MEDLINE
TI The hypercalcemia of malignancy: pathogenesis and management.
AU Mundy G R; Martin T J
SO METABOLISM: CLINICAL AND EXPERIMENTAL, (1982 Dec) 31 (12) 1247-77. Ref: 207
Journal code: MUM; 0375267. ISSN: 0026-0495.
AB The number of agents and treatment regimens which can be used in the medical treatment of hypercalcemia has increased markedly over the last 5 yr. As this list has increased, clinicians are anxious to know more about the humoral and cellular mechanisms which are responsible for the hypercalcemia of malignancy and to understand how these drugs work. Unfortunately there is no treatment available presently which is uniformally safe and effective, and the potential pathogenetic mechanisms responsible for hypercalcemia are hotly debated. In this review, we plan to summarize current views of the pathogenesis, clinical features and treatment of hypercalcemia associated with malignant disease.

L19 ANSWER 16 OF 21 MEDLINE
AN 82272175 MEDLINE
TI Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 37-1982. A three-month-old girl with optic atrophy and hepatomegaly.
AU Anonymous
SO NEW ENGLAND JOURNAL OF MEDICINE, (1982 Sep 16) 307 (12) 735-43.
Journal code: NOW; 0255562. ISSN: 0028-4793.

L19 ANSWER 17 OF 21 MEDLINE
AN 82039661 MEDLINE
TI Diagnosis of bone disease by core biopsies.
AU Gruber H E; Stauffer M E; Thompson E R; Baylink D J
SO SEMINARS IN HEMATOLOGY, (1981 Oct) 18 (4) 258-78. Ref: 43
Journal code: UN9; 0404514. ISSN: 0037-1963.

L19 ANSWER 18 OF 21 MEDLINE
AN 76153019 MEDLINE
TI [Recent progress in morphology and diagnosis of bone diseases and bone tumors (author's transl)].
Fortschritte in der Morphologie und Diagnostik von Osteopathien und Knochentumoren.
AU Delling G; Schulz A; Seifert G
SO RADIOLOGE, (1976 Feb) 16 (2) 46-53.
Journal code: QRL; 0401257. ISSN: 0033-832X.
AB 1. Bone structure is shaped by a specialized bone cell system comprising osteoblasts, osteocytes and osteoclasts. --2. The

function of this bone cell system is impaired by metabolic bone disease altering bone structure, bone mass and mineral content. --3. In metabolic bone disease a striking improvement in morphologic diagnosis could be obtained recently using undecalcified preparations of bone tissue as well as histomorphometric methods. --4. For exact diagnosis and successful therapy of bone tumors interdisciplinary cooperation is mandatory. The advantages of modern morphologic methods are proven helpful in diagnosing benign and malignant bone tumors.

L19 ANSWER 19 OF 21 MEDLINE
AN 74289730 MEDLINE
TI [Physiopathology of osteoporosis in the young adult]. Physiopathologie de l'osteoporose de l'adulte jeune.
AU Bordier P; de Seze S; Miravet L; Berbir N
SO SEMAINE DES HOPITAUX, (1974 Jan 14) 50 (3) 197-206. Journal code: ULD; 9410059.

L19 ANSWER 20 OF 21 MEDLINE
AN 72203552 MEDLINE
TI Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 29-1972.
AU Anonymous
SO NEW ENGLAND JOURNAL OF MEDICINE, (1972 Jul 20) 287 (3) 138-43. Journal code: NOW; 0255562. ISSN: 0028-4793.

L19 ANSWER 21 OF 21 MEDLINE
AN 70138463 MEDLINE
TI [Quantitative histological study of osteoclastic resorption in primary and secondary hyperparathyroidism]. Etude histologique quantitative de la resorption osteoclastique dans les hyperparathyroidies primitives et secondaires. A propos de 90 biopsies osseuses.
AU Meunier P; Vignon G; Vauzelle J L; Zech P
SO PATHOLOGIE BIOLOGIE, (1969 Nov) 17 (21) 927-38. Journal code: OSG; 0265365. ISSN: 0369-8114.

(FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI; SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 12:26:43 ON 21 MAY 2001)

L20 2992 S OGATA E?/AU Authors
L21 6933 S KOIZUMI M?/AU
L22 49892 S TAKAHASHI S?/AU
L23 36 S L20 AND L21 AND L22
L24 117 S L20 AND (L21 OR L22)
L25 55 S L21 AND L22
L26 59645 S L20 OR L21 OR L22
L27 15 S (L23 OR L24 OR L25 OR L26) AND L5
L28 5 DUP REM L27 (10 DUPLICATES REMOVED)

Searcher : Shears 308-4994

L28 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
ACCESSION NUMBER: 2000:145122 CAPLUS
DOCUMENT NUMBER: 132:175806
TITLE: Method for **diagnosing bone metastasis** of malignant **tumor**
INVENTOR(S): **Ogata, Etsuro; Koizumi, Mitsuru; Takahashi, Shunji**
PATENT ASSIGNEE(S): Japan
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000011480	A1	20000302	WO 1999-JP4480	19990820
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9953025	A1	20000314	AU 1999-53025	19990820

PRIORITY APPLN. INFO.: JP 1998-236146 A 19980821
WO 1999-JP4480 W 19990820

AB Therapeutic effects of drugs on bone metastasis and cancer (mammary cancer, prostatic cancer, lung cancer, etc.)-inducing bone metastasis are evaluated by using a marker reflecting the activity of **osteoblasts** and a marker reflecting the effect of **osteoclasts**, including bone alk. phosphatase, osteocalcin, type-I procollagen peptide fragments, and crossover index.

REFERENCE COUNT: 3
REFERENCE(S):
(1) Koizumi, M; CLINICAL CALSIUM 1998, P98
(2) Nakaba, K; Therapeutic Research 1995, V16(12), P212
(3) Takahashi, S; Biotherapy 1997, V11(1), P75

L28 ANSWER 2 OF 5 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998234725 EMBASE
TITLE: Bone metabolic markers in metastatic bone tumors.
AUTHOR: **Koizumi M.; Ogata E.**
CORPORATE SOURCE: M. Koizumi, Departments of Nuclear Medicine, Cancer

Institute Hospital, 1-37-1 Kami-Ikebukuro,
Toshima-ku, Tokyo 170-0012, Japan. mitsuru@jfcr.or.jp
SOURCE: Cancer Journal, (1998) 11/3 (137-140).
Refs: 34
ISSN: 0765-7846 CODEN: CANJEI
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Currently, the **diagnosis** of **bone metastasis** is performed using imaging techniques. Recently however, bone metabolic markers have been evaluated as possible **diagnostic** and monitoring methods for **metastatic bone** disease. **Bone** metabolic markers are classified as either resorption or formation markers. Each marker has its own biological signifiCanCe and hence a different clinical relevance. Clinical problems involving **bone metastasis**, for example cost-effectiveness in **screening** and difficulties in monitoring response, may be solved by the application of bone metabolic markers. The current situation concerning the use of bone metabolic markers in metastatic bone disease can be summarized as follows: 1. Bone metabolic markers are not yet established as **screening** methods for **bone metastasis**. 2. **Bone** metabolic markers are well- established in monitoring responses to both conventional and bisphosphonate therapies. 3. Measurement of bone metabolic markers can provide an insight into the mechanisms of bone metastasis.

L28 ANSWER 3 OF 5 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 97087361 EMBASE
DOCUMENT NUMBER: 1997087361
TITLE: Significance of bone metabolic markers for **diagnosis** of **bone metastasis**.
AUTHOR: **Takahashi S.; Koizumi M.**
CORPORATE SOURCE: Dr. S. Takahashi, Cancer Institute Hospital, Japanese Found. for Cancer Research, 1-37-1 Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan
SOURCE: Biotherapy, (1997) 11/1 (75-80).
Refs: 17
ISSN: 0914-2223 CODEN: BITPE
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
033 Orthopedic Surgery

LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese

AB The most common procedure for **diagnosis** of **bone metastasis** is **bone** scintigraphy, but it has the disadvantages of high cost and failure to evaluate therapy response. Recently, several new bone metabolic markers have been developed and applied for **diagnosis** of **bone metastasis**. Most of these markers were reviewed, and bone alkaline phosphatase (among bone formation markers) and some collagen cross link metabolites (among bone resorption markers) seem to be most promising. We have investigated the efficacy of several bone metabolic markers: serum carboxy-terminal telopeptide of type 1 collagen (1CTP) and urinary free deoxypyridinoline (fDPD) as bone resorption markers; and serum carboxy-terminal propeptide of type 1 collagen (P1CP), osteocalcin (OC), total alkaline phosphatase (ALP), and bone alkaline phosphatase (BAP) as bone formation markers for **diagnosis** of **bone metastasis** of prostate (**osteoblastic** type), lung (osteolytic type), and breast (mixed type) cancer. In patients with prostate cancer, BAP was most useful for **diagnosis** of **bone metastasis**, but **bone** resorption markers also increased. In follow up, 1CTP was most useful for predicting response to therapy, and more useful than prostate-specific antigen (PSA). In patients with lung cancer, bone resorption markers seemed more useful than bone formation markers for **diagnosis** and follow-up of **bone metastasis**. In patients with breast **cancer**, 1CTP was most effective for **diagnosis** of **bone metastasis** because of no increase in postmenopausal osteoporosis. Combination of resorption and formation markers increased sensitivity. In follow up, bone metabolic markers seemed more useful for predicting therapeutic response of bone metastasis than CEA or CA 15-3. These findings suggest that bone metabolic markers would be useful not only to **detect** **bone metastases** but also to monitor therapeutic effect, and they could partly substitute for bone scintigraphy.

L28 ANSWER 4 OF 5 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 96416927 MEDLINE
DOCUMENT NUMBER: 96416927 PubMed ID: 8819718
TITLE: Serum concentration of pyridinoline cross-linked carboxy-terminal telopeptide of type-I collagen (ICTP) and carboxyterminal propeptide of human type I procollagen (PICP) in the **diagnosis** of **bone metastases**.
AUTHOR: **Koizumi M**; Yamada Y; Takiguchi T; Suzuki C; Akashi T; Nomura E; Yamashita T; **Ogata E**
CORPORATE SOURCE: Department of Nuclear Medicine, Cancer Institute Hospital, Japan.

Searcher : Shears 308-4994

SOURCE: KAKU IGAKU [JAPANESE JOURNAL OF NUCLEAR MEDICINE], (1996 Jan) 33 (1) 77-84.
Journal code: KML; 2985202R. ISSN: 0022-7854.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961127

AB Recently discovered bone metabolic markers are expected to play an additional role in the **diagnosis** of **bone metastasis**. We measured **bone** metabolic markers, serum pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen (ICTP) and carboxyterminal propeptide of human type I procollagen (PICP) in 224 patients with breast cancer (106 with bone metastases), 61 patients with prostatic cancer (30 with bone metastases), 45 patients with lung cancer (17 with bone metastases) and 13 patients with miscellaneous cancers (7 with bone metastasis) and compared the values in the presence and absence of bone metastasis. ICTP and PICP increased significantly in patients with bone metastases. By the analysis of sensitivity and specificity, the cut-off levels were considered to be 5.0 ng/ml for ICTP and 140 ng/ml for PICP. In lung cancer (bone metastases are mostly of osteolytic), ICTP was excellent marker in **detecting bone metastasis**. In breast **cancer** (**bone metastases** are mostly of mixed type), ICTP was good in **detecting bone metastases**. In prostatic **cancer** (**bone metastases** are mostly of **osteoblastic**), ICTP and PICP were good markers in **detecting** high grade of **bone metastases**. Over all, ICTP was more sensitive in the **diagnosis** of **bone metastases** than PICP. However, both markers were not effective in **detecting** low grade **bone metastases**. ICTP and PICP should play a supportive role to imaging modalities in the **diagnosis** of **bone metastases**.

L28 ANSWER 5 OF 5 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 96034006 MEDLINE
DOCUMENT NUMBER: 96034006 PubMed ID: 7559734
TITLE: Bone metabolic markers in bone metastases.
AUTHOR: **Koizumi M**; Yamada Y; Takiguchi T; Nomura E; Furukawa M; Kitahara T; Yamashita T; Maeda H; **Takahashi S**; Aiba K; +
CORPORATE SOURCE: Department of Nuclear Medicine, Cancer Institute Hospital, Tokyo, Japan.

SOURCE: JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, (1995) 121 (9-10) 542-8.
Journal code: HL5; 7902060. ISSN: 0171-5216.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19951227
Entered Medline: 19951122

AB The efficacy and cost/performance benefit of radionuclide bone scintigraphy in monitoring metastatic bone activity remain controversial. Recently developed bone metabolic markers are expected to play an additional role in the **diagnosis** of **bone metastasis**. We measured **osteoclastic** and **osteoblastic** markers in 267 patients with breast cancer (100 with bone metastasis), 38 patients with prostatic cancer (25 with bone metastasis), 50 patients with lung cancer (12 with bone metastasis) and 33 patients with miscellaneous cancers (13 with bone metastasis) and compared the values in the presence and absence of bone metastasis. Bone metabolic markers, both **osteoclastic** and **osteoblastic**, increased significantly in patients with bone metastasis. In breast cancer (bone metastasis is mostly of the mixed type), **osteoclastic** markers were good in **detecting bone metastasis**. In prostatic **cancer** (**bone metastasis** is mostly **osteoblastic**), **osteoclastic** and **osteoblastic** markers were equally effective in **detecting bone metastasis**. In lung **cancer** (**bone metastasis** is mostly osteolytic), **osteoclastic** markers were elevated preferentially in bone metastasis. Over all, **osteoclastic** markers were more sensitive in the **diagnosis** of **bone metastasis**, and among **osteoclastic** markers, serum pyridionoline-cross-linked carboxyterminal telopeptide was the most efficient in both specificity (91.0%) and sensitivity (48.6%) for **detecting bone metastasis**.

FILE 'HOME' ENTERED AT 12:32:07 ON 21 MAY 2001

FILE 'CAPLUS' ENTERED AT 15:17:15 ON 21 MAY 2001

L1 1509 SEA FILE=CAPLUS ABB=ON PLU=ON (TYPE(W)(1 OR I))(3A)(PRO COLLAGEN OR PRO COLLAGEN)

L2 7046 SEA FILE=CAPLUS ABB=ON PLU=ON BONE(5A)(METAST? OR CANCER? OR CARCIN? OR TUMOUR OR TUMOR OR NEOPLAS?)

L3 436 SEA FILE=CAPLUS ABB=ON PLU=ON L2(5A)(DIAGNOS? OR DETERM? OR DETECT? OR DET## OR SCREEN?)

L4 26 SEA FILE=CAPLUS ABB=ON PLU=ON L3 AND (OSTEOBLAST? OR OSTEOCLAST? OR OSTEO(W)(BLAST? OR CLAST?))

L5 5 SEA FILE=CAPLUS ABB=ON PLU=ON L1 AND L4

L1 1509 SEA FILE=CAPLUS ABB=ON PLU=ON (TYPE(W)(1 OR I))(3A)(PRO COLLAGEN OR PRO COLLAGEN)

L6 9918 SEA FILE=CAPLUS ABB=ON PLU=ON BONE(S)(METAST? OR CANCER? OR CARCIN? OR TUMOUR OR TUMOR OR NEOPLAS?)

L7 1017 SEA FILE=CAPLUS ABB=ON PLU=ON L6(S)(DIAGNOS? OR DETERM? OR DETECT? OR DET## OR SCREEN?)

L8 78 SEA FILE=CAPLUS ABB=ON PLU=ON L7 AND (OSTEOBLAST? OR OSTEOCLAST? OR OSTEO(W)(BLAST? OR CLAST?))

L9 7 SEA FILE=CAPLUS ABB=ON PLU=ON L1 AND L8

L10 7 L5 OR L9

L10 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:444520 CAPLUS

DOCUMENT NUMBER: 133:308371

TITLE: Biochemical markers and skeletal metastases

AUTHOR(S): Demers, Laurence M.; Costa, Luis; Lipton, Allan

CORPORATE SOURCE: Departments of Medicine and Pathology, The Penn State University College of Medicine, Hershey, PA, 17033-0850, USA

SOURCE: Cancer (N. Y.) (2000), 88(12, Suppl.), 2919-2926
CODEN: CANCAR; ISSN: 0008-543X

PUBLISHER: John Wiley & Sons, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Skeletal metastases are common occurrences in patients with malignancies such as breast and prostate carcinoma, but they are difficult to diagnose nonradiol., and treatment is difficult to follow clin. Recent developments suggest that biochem. markers of bone remodeling, such as the bone collagen breakdown product N-telopeptide and the bone formation marker known as bone specific alk. phosphatase, hold great promise as clin. tools for the management of patients with metastatic bone disease. Serum levels of the **bone** formation marker known as **bone** specific alk. phosphatase (BAP), along with serum levels of the

bone collagen breakdown product carboxyterminal telopeptide of Type I collagen (ICTP) and urine levels of pyridinoline (PYD), deoxypyridinoline (DPD), and N-telopeptide (NTx), were measured in a large cohort of patients with newly **diagnosed** or progressive **cancer** of the breast, prostate, lung, and other sites. Bone marker levels were correlated with the presence or absence of bone scan-documented metastases; metastatic disease extension in terms of the no. of skeletal sites involved; and the type of lesion, whether blastic or lytic. Sites examd. included the pelvis, spine, skull, ribs, and long bones. All of the bone markers examd., including BAP and NTx, were abnormally elevated in a high proportion of patients with confirmed metastases to bone. Urine NTx levels and bone specific alk. phosphatase were significantly correlated with the no. of skeletal sites involved, and a significant correlation between marker level and extent of skeletal involvement was also obsd. In addn., both markers were higher in patients with a blastic disease presentation than in patients with osteolytic lesions. Biochem. markers of bone resorption and bone formation are abnormally raised in the blood and urine of patients with metastatic bone disease. Markers of bone collagen breakdown, such as N-telopeptide, as well as markers of **osteoblast** function, such as bone specific alk. phosphatase, appear to be of use in assessing and managing patients with malignancies that metastasize to bone. In this study, both NTx and BAP showed a significant correlation with both the presence of bone metastases and the extent of skeletal involvement. Biochem. markers of **bone** remodeling can also be used to guide decision making regarding the treatment of **metastatic bone** disease and to **det.** the effectiveness of therapy for patients with **cancer** to **bone** whose broad-based symptoms make it difficult to discern true response to therapy.

L10 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER:	2000:257017 CAPLUS
DOCUMENT NUMBER:	132:263359
TITLE:	Biochemical markers of bone metabolism reflect **osteoclastic** and **osteoblastic** activity in multiple myeloma
AUTHOR(S):	Abildgaard, N.; Glerup, H.; Rungby, J.; Bendix-Hansen, K.; Kassem, M.; Brixen, K.; Heickendorff, L.; Nielsen, J. L.; Eriksen, E. F.
CORPORATE SOURCE:	Department of Haematology, Aarhus University Hospital, Aarhus, DK-8000, Den.
SOURCE:	Eur. J. Haematol. (2000), 64(2), 121-129 CODEN: EJHAEC; ISSN: 0902-4441
PUBLISHER:	Munksgaard International Publishers Ltd.
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB To evaluate the use of recently developed assays of bone metab. in multiple myeloma the authors performed a histomorphometric study of bone biopsies in 16 myeloma patients. Furthermore, the authors measured the levels of interleukin(IL)-6, sol. IL-6 receptor (IL-6sR), IL-1.beta., tumor necrosis factor (TNF) .alpha., TNF.beta., and transforming growth factor (TGF) .beta. in marrow plasma aspirated from the biopsy area. The N-terminal telopeptide of collagen I (Ntx) in urine showed a strong pos. correlation with the dynamic histomorphometric indexes of bone resorption (r = 0.68-0.72). Slightly weaker correlations were obsd. between the dynamic indexes of bone resorption and the C-terminal telopeptide of collagen I (ICTP) in serum (r = 0.57-0.62) and deoxypyridinoline (Dpyr) in urine (r = 0.54), whereas urinary pyridinoline (Pyr) did not correlate with the histomorphometric findings. Blood serum C-terminal propeptide of procollagen I (PICP) and serum bone-specific alk. phosphatase (bAP) showed significant correlations with the dynamic parameters of bone formation (r = 0.57-0.58), whereas serum osteocalcin and serum total AP did not. Highly significant correlations were obsd. between marrow IL-6 and rates of bone resorption and activation frequency (r = 0.76-0.82) and with serum ICTP (r = 0.63). Minor, but also significant correlations were obsd. between the resorptive indexes and IL-6sR and IL-1.beta.. These data indicate that measurements of the biochem. markers of bone metab. may be useful in monitoring myeloma bone disease, and might thus be of use for dose titrn. of bisphosphonate therapy.

REFERENCE COUNT: 43

REFERENCE(S):

(2) Abildgaard, N; Br J Haematol 1997, V96, P103 CAPLUS
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(9) Behr, W; Clin Chem 1986, V32, P1960 CAPLUS
(10) Berenson, J; N Engl J Med 1996, V334, P488 CAPLUS
(11) Brincker, H; Br J Haematol 1998, V101, P280 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:145122 CAPLUS

DOCUMENT NUMBER: 132:175806

TITLE: Method for **diagnosing bone metastasis** of malignant **tumor**

INVENTOR(S): Ogata, Etsuro; Koizumi, Mitsuru; Takahashi, Shunji

PATENT ASSIGNEE(S): Japan

SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000011480	A1	20000302	WO 1999-JP4480	19990820
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9953025	A1	20000314	AU 1999-53025	19990820

PRIORITY APPLN. INFO.: JP 1998-236146 A 19980821
WO 1999-JP4480 W 19990820

AB Therapeutic effects of drugs on bone metastasis and cancer (mammary cancer, prostatic cancer, lung cancer, etc.)-inducing bone metastasis are evaluated by using a marker reflecting the activity of **osteoblasts** and a marker reflecting the effect of **osteoclasts**, including bone alk. phosphatase, osteocalcin, **type-I procollagen** peptide fragments, and crossover index.

REFERENCE COUNT: 3
REFERENCE(S):
(1) Koizumi, M; CLINICAL CALSIUM 1998, P98
(2) Nakaba, K; Therapeutic Research 1995, V16(12), P212
(3) Takahashi, S; Biotherapy 1997, V11(1), P75

L10 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:107788 CAPLUS
DOCUMENT NUMBER: 128:255742
TITLE: Monitoring of multiple myeloma patients by simultaneously measuring marker substances of bone resorption and formation
AUTHOR(S): Withold, Wolfgang; Arning, Michael; Schwarz, Martin; Wolf, Hans-Heinrich; Schneider, Wolfgang
CORPORATE SOURCE: Institut fur Klinische Chemie und Laboratoriumsdiagnostik, Heinrich-Heine-Universitat, Moorenstrasse 5, Dusseldorf, D-40225, Germany
SOURCE: Clin. Chim. Acta (1998), 269(1), 21-30
CODEN: CCATAR; ISSN: 0009-8981
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Fifteen patients (13 males and two females; mean age, 63 yr; age range, 46-84 yr) with multiple myeloma were studied prospectively (range of follow-up period, 2-6 mo) to elucidate the diagnostic validity of biochem. markers of bone formation (bone alk. phosphatase and the C-terminal propeptide of **type I procollagen**) and bone resorption (urinary excretion of pyridinium cross-links) for monitoring these patients. Eleven of 15 patients received melphalan i.v. and prednisone p.o. every 4 wk. All patients were given pamidronate i.v. for inhibition of bone resorption. The mean values of the urinary excretion of pyridinium cross-links were significantly higher in the patients fulfilling the criteria of 'progression' or 'relapse' than in those showing 'response' and those in the 'plateau phase' ($P<0.05$). In contrast, neither bone alk. phosphatase nor C-terminal propeptide serum values differed significantly between these two groups ($P<0.05$). The concns. of both bone formation markers were significantly lower in the patients than in the samples obtained from apparently healthy persons ($P<0.001$). There was a significant inverse correlation between the no. of pamidronate courses and the serum concns. of bone alk. phosphatase ($P<0.05$). A lack of correlation was obsd. between the urinary excretion of pyridinium cross-links and all other lab. parameters measured (serum concns. of total protein, calcium, creatinine and .beta.2-microglobulin). In conclusion, the urinary excretion of pyridinium cross-links might be a useful parameter for monitoring multiple myeloma patients. Decreased values of bone formation markers may be due to a suppressive effect of the bisphosphonate agents administered or reflect the severity of osteolytic lesions which have been described as being assocd. with unbalanced bone remodelling.

L10 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:734097 CAPLUS

DOCUMENT NUMBER: 128:33060

TITLE: Comparison of Assay of Total and Bone-Specific Alkaline Phosphatase in the Assessment of **Osteoblast** Activity in Patients with Metastatic Bone Disease

AUTHOR(S): Piovesan, A.; Berruti, A.; Torta, M.; Cannone, R.; Sperone, P.; Panero, A.; Gorzegno, G.; Termine, A.; Dogliotti, L.; Angeli, A.

CORPORATE SOURCE: Ospedale San Luigi Gonzaga, Oncologia Medica, Clinica Medica, Centro Interdipartimentale per lo Studio e la Cura delle Osteopatie Metaboliche, Regione Gonzole 10, Orbassano, Turin, 10043, Italy

SOURCE: Calcif. Tissue Int. (1997), 61(5), 362-369
CODEN: CTINDZ; ISSN: 0171-967X

PUBLISHER: Springer-Verlag New York Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The evaluation of response of osseous metastases to systemic treatments is often low as a consequence of the different radiol. appearances that make objective assessment not only difficult but sometimes impossible. Radiog. evidence of recalcification, the UICC criterion of response, is often evident for 6 mo and sometimes may be delayed even more. This accounts for lower response rates in bone with respect to other metastatic sites in clin. trials. A transient rise in bone formation indexes may provide an early indication of bone healing and, along with measurement of symptomatic changes, could ameliorate the response evaluation. Among the biochem. markers of bone formation, total alk. phosphatase (TALP) is widely employed, but it lacks specificity. Estn. of bone isoenzyme (E-BALP) by electrophoretic techniques is time consuming and semiquant. The immunoradiometric assay (I-BALP) seems to overcome these limitations. In this study, the authors compared the two methods of bone isoenzyme estn. with each other and with the levels of bone gla protein (BGP) and carboxy-terminal propeptide of **type I procollagen** (PICP) in a group of 136 cancer patients with bone metastases stratified as having lytic or mixed and blastic lesions at x-ray, and in 62 cancer patients without apparent bone involvement. The same indexes were also evaluated prospectively in a patient subset submitted to chemotherapy assocd. with pamidronate. The aims of the study were to evaluate whether I-BALP is superior to E-BALP and whether both methods of bone isoenzyme estn. are more advantageous than TALP, BGP, and PICP in the assessment of **osteoblast** activity either in baseline conditions or in response to treatment. In bone metastatic patients with lytic appearances, values above the cut-off limit were obsd. in 32.1, 23.3, 48.9, 32.9, and 14 for, TALP, E-BALP, I-BALP, PICP, and BGP, while the corresponding percentages in those with blastic/mixed appearances were 74.0, 84.8, 76.9, 51.9, and 43.8, resp. In the patients without bone involvement, values within the normal range were 90.2, 98.2, 89.6, 71.7, and 90.2, resp. Levels of TALP, E-BALP, and I-BALP were reciprocally correlated in the three groups examd. In bone metastatic patients, however, the degree of correlation of the enzymes with PICP and BGP was weak. Liver isoenzyme of alk. phosphatase (LALP) was found to correlate with E-BALP, but not with I-BALP, in patients with mixed/blastic lesions. Thirty-eight patients were submitted to pamidronate therapy (60 mg every 3 wk, administered 4 times) in assocn. with cytotoxic treatment. **Osteoblastic** markers were detd. before any administration. Serum TALP, E-BALP, and I-BALP showed a transient rise in 9 cases, a progressive redn. in 12, no change in 2, and a progressive increase in 6. Changes in E-BALP and I-BALP from baseline were greater than those of TALP. A divergent pattern

between TALP and both I-BALP and E-BALP was found in 9 patients, whereas a divergent temporal profile between the two methods of bone isoenzyme estn. was recorded in only 3 patients. Eight out of 38 cases obtained a partial recalcification of lytic and mixed lesions. Seven of them showed the concomitant early increase in TALP, E-BALP, and I-BALP followed by a gradual decline (**osteoblastic** flare), whereas 1 patient demonstrated the flare of E-BALP and I-BALP but not of TALP. No relation was found between response and temporal changes in BGP and PICP serum levels. The authors conclude that I-BALP is a useful marker for **detecting** excess **osteoblastic** activity in patients who have at imaging "pure" lytic **bone metastases**. In the longitudinal evaluation of patients receiving multiple pamidronate infusions plus chemotherapy, TALP, E-BALP, and I-BALP, but not BGP and PICP, appeared to be useful to identify responders in bone. A slight advantage of measurements of serum bone isoenzyme (by both techniques) over TALP is apparent, but this study fails to demonstrate a clear superiority of I-BALP over E-BALP.

L10 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:26686 CAPLUS
DOCUMENT NUMBER: 126:141664
TITLE: Bone sialoprotein in serum of patients with malignant bone diseases
AUTHOR(S): Withold, Wolfgang; Armbruster, Franz P.; Karmatschek, Markus; Reinauer, Hans
CORPORATE SOURCE: Inst. Klinische Chemie, Heinrich-Heine-Univ. Duesseldorf, Duesseldorf, 40225, Germany
SOURCE: Clin. Chem. (Washington, D. C.) (1997), 43(1), 85-91
CODEN: CLCHAU; ISSN: 0009-9147
PUBLISHER: American Association for Clinical Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bone sialoprotein (BS), a protein synthesized by **osteoblasts** and **osteoclasts** and highly modified posttranslationally, constitutes a predominant fraction of the noncollagenous org. matrix in human bone. We report an assessment of serum concns. of BS detd. by RIA in patients with malignant bone diseases. In patients with bone metastases (according to scintigraphic criteria), serum BS concns. were greater than in patients without bone metastases. However, ROC curve anal. revealed that serum BS was inferior to serum bone alk. phosphatase in discriminating between patients with and without bone metastases. Patients with bone metastases showed a weak correlation between serum BS concns. and bone formation markers. Only "traditional" markers of bone formation, but not BS, were correlated with urinary deoxypyridinoline. Liver and kidney dysfunction had no significant influence on BS values in these

patients (as assessed by anal. of variance). In multiple myeloma patients treated with corticosteroids and bisphosphonates, BS concns. were lower than in tumor patients without bone metastases, and the correlation between BS concns. and the no. of bisphosphonate courses applied was significant. In postmenopausal women, serum BS concns. averaged 142% greater than in premenopausal women. Further studies should be done, therefore, to elucidate whether serum BS is able to predict high bone turnover after menopause.

L10 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:172747 CAPLUS
DOCUMENT NUMBER: 124:255111
TITLE: New and traditional serum markers of **bone** metabolism in the **detection** of skeletal **metastases**
AUTHOR(S): Plebani, M.; Bernardi, D.; Zaninotto, M.; De Paoli, M.; Secchiero, S.; Sciacovelli, L.
CORPORATE SOURCE: Azienda Ospedaliera di Padova, Department Laboratory Medicine, Padua, 35128, Italy
SOURCE: Clin. Biochem. (1996), 29(1), 67-72
CODEN: CLBIAS; ISSN: 0009-9120
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The evaluation of "new" and "traditional" markers of **osteoblastic** and **osteoclastic** activity, in patients with bone metastases. Our series consist of 40 patients with clin., radiol., and scintigraphic evidence of bone metastases, and 40 age-matched healthy subjects. In all samples, traditional markers were evaluated by measuring total alk. phosphatase (ALP), tartrate-resistant acid phosphatase (TrACP) activity, and osteocalcin (BGP) concn. To assess new biochem. bone markers, bone isoenzyme of alk. phosphatase (ALP-B) activity, carboxyterminal propeptide of **type I procollagen** (PICP), and carboxyterminal telopeptide of type I collagen (ICTP) concns. were measured. Our finding showed that the best diagnostic efficiency is provided by ICTP (0.94) followed by total ALP (0.90), ALP-B (0.80), and TrACP (0.76). The efficiency of BGP and PICP was, instead, very low (0.64 and 0.60, resp.). Our results confirm the utility of the new serum markers such as ALP-B and ICTP assays in **detecting bone metastases.**

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 15:30:18 ON 21 MAY 2001)
L11 29 S L5
L12 9 DUP REM L11 (20 DUPLICATES REMOVED)

L12 ANSWER 1 OF 9 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:531162 BIOSIS

DOCUMENT NUMBER: PREV200000531162
TITLE: Type I collagen metabolism (PINP, ICTP) in health and disease.
AUTHOR(S): Risteli, J. (1)
CORPORATE SOURCE: (1) Department of Clinical Chemistry, University of Oulu, Oulu Finland
SOURCE: Tumor Biology, (September, 2000) Vol. 21, No. Supplement 1, pp. 24. print.
Meeting Info.: 28th Meeting of the International Society for Oncodevelopmental Biology and Medicine Munich, Germany September 08-13, 2000
ISSN: 1010-4283.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L12 ANSWER 2 OF 9 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:12511 BIOSIS
DOCUMENT NUMBER: PREV200000012511
TITLE: Suppressive effects of bisphosphonate on bone resorption induced by murine sarcoma.
AUTHOR(S): Kamioka, Hiroaki (1); Osaka, Shunzo; Suzuki, Koyu; Ryu, Junnosuke
CORPORATE SOURCE: (1) Department of Orthopaedic Surgery, Nihon University School of Medicine, 30-1 Oyaguchi Kamimachi, Itabashi-ku, Tokyo, 173-8610 Japan
SOURCE: Nihon University Journal of Medicine, (June, 1999) Vol. 41, No. 3, pp. 121-133.
ISSN: 0546-0352.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We carried out an experimental study on the effects of bisphosphonate (BPS), a substance inhibitory to **osteoclasts**, on osteolytic lesions caused by malignant bone tumors. Osteolytic tumors were induced in the femurs of mice by an injection of ascites sarcoma 180 suspension. BPS was introduced subcutaneously into the backs. The subsequent changes in the femur were examined radiologically and histopathologically. Measurements were also made of the type procollagen C-terminal peptide (P CP) in the serum, an osteoplastic marker, and the urine pyridinoline, a bone resorption marker. As a result, the radiograms showed that BPS administration inhibited the osteolytic changes in the **bone tumors**. Histopathological examinations **detected** calcification in the lesions. The average P CP level was 689.7 +- 182 ng/ml in the bone tumor group and 38.3 +- 18 ng/ml in the BPS-administered group. The average pyridinoline level was estimated to be 464 +- 103.8 nmol/mmol creatinine in the f ormer group and

67.5 +- 12.8 nmol/mmol creatinine in the latter group. Both differences were statistically significant. The present findings thus indicated that administration of BPS inhibited bone resorption in malignant tumors.

L12 ANSWER 3 OF 9 JICST-EPlus COPYRIGHT 2001 JST
ACCESSION NUMBER: 971020182 JICST-EPlus
TITLE: Significance of Carboxyterminal Propeptide of **Type I Procollagen**(PICP) and Carboxyterminal Telopeptide of Type I Collagen(ICTP) in Patients with Prostate Cancer.
AUTHOR: KOGA HIROFUMI; NAITO SEIJI; HASEGAWA SHUJI; NOMA HIDEYA; YAMAZAKI TAKENARI; NAKAJIMA MICHITAKA; KUMAZAWA JOICHI
CORPORATE SOURCE: Kyushu Univ., Fac. of Med.
SOURCE: Ther Res, (1997) vol. 18, no. 10, pp. 3274-3280.
Journal Code: Y0681A (Tbl. 7, Ref. 17)
ISSN: 0289-8020
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: Japanese
STATUS: New
AB Recently bone metabolic markers are expected to play an additional role in the **diagnosis** of **bone metastasis**. Carboxyterminal propeptide of **type I procollagen**(PICP) is regard to be one of osteoplastic markers and carboxyterminal telopeptide of type I collagen(ICTP) are thought to be one of **osteoblastic** markers. We measured serum level of PICP and ICTP in 60 patients with prostate cancer and in 44 patients with benign prostate hyperplasia(BPH). Of 60 patients with prostate cancer, 10 were those with newly **diagnosed** prostate **cancer** with **bone metastasis** (group A), 6 were patients with relapsed metastatic bone lesions(group B), 6 were those with relapsed prostate cancer but stable metastatic bone lesions(group C), 12 were those with stable metastatic bone lesion after treatment(group D), 26 were those without bone metastasis(stage B and C prostate cancer)(group E) and 44 were diagnossed clinicaly as BPH(group F). The PICP and ICTP levels in patients of group A and B were significantly higher than those in patients of group C,D,E and F, respectively. A good correlation was observed between the serum level of alkaline phosphatase(ALP)(.GAMMA.=0.8956 and 0.6947, respectively). Moreover PICP and ICTP levels in patients with extent of disease(EOD) grade 3 bone lesions were significantly higher than those in patients with EOD grade 0,1 and 2 bone lesions. Consequtive measurement of these markers during the initial 12 weeks after commencing the hormonal treatment indicated that there was little change in both PICP and ICTP levels in patients of group E, whereas various types of

fluctuation were observed in patients of group A. In conclusion, the serum levels of PICP and ICTP seem to be a useful, non-invasive markers to assess the metastasis in patient with prostate cancer, but further evaluation is necessary to estimate the effect of treatment. (author abst.)

L12 ANSWER 4 OF 9 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 97361110 MEDLINE
DOCUMENT NUMBER: 97361110 PubMed ID: 9218004
TITLE: Serum markers of bone metastases in postmenopausal breast cancer patients treated with formestane.
AUTHOR: Martinetti A; Bajetta E; Seregni E; Zilembo N; Ferrari L; Noberasco C; Massaron S; Rimassa L; Bombardieri E
CORPORATE SOURCE: Nuclear Medicine Division, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.
SOURCE: TUMOUR BIOLOGY, (1997) 18 (4) 197-205.
Journal code: TUB; 8409922. ISSN: 0289-5447.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970812
Last Updated on STN: 19980206
Entered Medline: 19970731

AB Bone metabolism marker evaluation is expected to play an auxiliary role in the **diagnosis** and follow-up of **bone metastases** in patients affected by different types of neoplasms. In this study we have evaluated **osteoblastic** and **osteoclastic** markers in 18 patients with **bone metastases** from breast **cancer** at **diagnosis** and for 1 year of follow-up during treatment with the aromatase inhibitor formestane. **Osteoblastic** markers include the carboxy-terminal propeptide of **type I procollagen**, the bone-specific alkaline phosphatase and the bone GLA protein. The carboxy-terminal cross-linked telopeptide of type I collagen (ICTP) was evaluated as a marker of **osteoclastic** activity. The patients were classified into three groups according to clinical response. A good correlation between marker level modifications and clinical evolution of skeletal metastases was observed for all the examined markers. Patients with progressive disease showed increasing levels of all markers, whereas patients in regression showed a reduction compared to the basal levels; patients with stable disease fell in between these two categories. We also found that basal ICTP values have prognostic significance: in the stable and progressive disease group they were higher than in the partial response group.

L12 ANSWER 5 OF 9 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 96262145 MEDLINE
DOCUMENT NUMBER: 96262145 PubMed ID: 8664134
TITLE: Biochemical evaluation of bone turnover in cancer patients with bone metastases: relationship with radiograph appearances and disease extension.
AUTHOR: Berruti A; Piovesan A; Torta M; Raucci C A; Gorzegno G; Paccotti P; Dogliotti L; Angeli A
CORPORATE SOURCE: Centro Interdipartimentale per lo Studio delle Osteopatie Metaboliche, Universita di Torino, Ospedale San Luigi Gonzaga, Turin, Italy.
SOURCE: BRITISH JOURNAL OF CANCER, (1996 Jun) 73 (12) 1581-7. Journal code: AV4; 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960819
Last Updated on STN: 19980206
Entered Medline: 19960806

AB Serum bone alkaline phosphatase (BALP), serum carboxy-terminal propeptide of **type I procollagen** (PICP) and serum bone gla protein (BGP) as markers of bone formation, serum carboxy-terminal telopeptide of type I collagen (ICTP) as a marker of collagen resorption and fasting molar ratio of urinary calcium to creatinine (CaCr) and serum parathyroid hormone (PTH) were determined in two groups of cancer patients: 48 with advanced or metastatic disease with negative bone scan and 174 with bone metastases categorised as having lytic, mixed or blastic lesions and with more or fewer than or equal to three sites involved. In patients without apparent bone involvement, bone formation markers were rarely elevated. Conversely, serum ICTP was frequently found to be supranormal, showing it to be a non-specific marker for early **detection** of **bone metastases**. As expected, values of **bone** formation markers progressively increased in patients with lytic, mixed and blastic lesions, but ICTP levels did not show any differences according to the types of bone appearances, confirming previous reports of elevated **osteoclast** activity also in patients with apparent blastic lesions. Serum PTH increased significantly in patients with lytic compared with patients with mixed and blastic appearances, paralleling the bone formation markers, but CaCr showed the opposite pattern. These data are compatible with calcium entrapment in the bone in patients with increased **osteoblast** activity. This so called 'bone hunger syndrome' is further confirmed by the finding that in the subgroup of blastic appearances CaCr

diminished whereas both ICTP and PTH increased according to the extent of tumour load in the bone.

L12 ANSWER 6 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96140763 EMBASE
DOCUMENT NUMBER: 1996140763
TITLE: [Biochemical markers of bone metabolism in metastatic bone disease].
BIOCHEMISCHE MARKER DES KNOCHENSTOFFWECHSELS BEI KNOCHENMETASTASEN.
AUTHOR: Seyfried C.; Seibel M.J.; Woitge H.W.; Pecherstorfer M.; Ziegler R.
CORPORATE SOURCE: Medizinische Klinik I, Universitat Heidelberg, Bergheimer Str. 58,D-69115 Heidelberg, Germany
SOURCE: Klinisches Labor, (1996) 42/4 (257-267).
ISSN: 0941-2131 CODEN: KLLAEA
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry
033 Orthopedic Surgery
LANGUAGE: German
SUMMARY LANGUAGE: German; English

AB Biochemical markers of bone metabolism can be valuable tools for the diagnosis, follow-up control and aftercare of metastatic bone disease. Parameters of bone resorption (hydroxyproline, pyridinium crosslinks, tartrate-resistant acid phosphatase or hypercalciuria) are the most important ones since they reflect the destructive character of invasive bone metastases, either directly or indirectly. Most of the experience has been gained by using urinary hydroxyproline, which allows a relatively precise estimation of the osteclastic activity of bone metastases. Pyridinium crosslinks and urinary calcium excretion seem to be useful markers for the **diagnosis** of **bone metastases** and for therapeutical monitoring. Both are complementary parameters of the metabolism of the collagen matrix and that of the mineralized compartment of bone. On the side of bone formation markers, serum osteocalcin (OC) plays an important role in the diagnosis and follow-up and, in the case of multiple myeloma, also as a prognostic indicator. In contrast, no predictive value has been demonstrated so far for any of the other parameters. The clinical importance of bone-specific alkaline phosphatase and of the amino-and carboxyterminal **type** I and III **procollagen** propeptides remains to be proven in further clinical studies. They might be of advantage in the early diagnosis of medullary metastatic disease, that is to say the stage of the metastasizing process preceding osteolysis.

L12 ANSWER 7 OF 9 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 96416927 MEDLINE
DOCUMENT NUMBER: 96416927 PubMed ID: 8819718
TITLE: Serum concentration of pyridinoline cross-linked carboxy-terminal telopeptide of type-I collagen (ICTP) and carboxyterminal propeptide of human **type I procollagen** (PICP) in the **diagnosis** of **bone metastases**.
AUTHOR: Koizumi M; Yamada Y; Takiguchi T; Suzuki C; Akashi T; Nomura E; Yamashita T; Ogata E
CORPORATE SOURCE: Department of Nuclear Medicine, Cancer Institute Hospital, Japan.
SOURCE: KAKU IGAKU [JAPANESE JOURNAL OF NUCLEAR MEDICINE], (1996 Jan) 33 (1) 77-84.
Journal code: KML; 2985202R. ISSN: 0022-7854.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
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Entered Medline: 19961127

AB Recently discovered bone metabolic markers are expected to play an additional role in the **diagnosis** of **bone metastasis**. We measured **bone** metabolic markers, serum pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen (ICTP) and carboxyterminal propeptide of human **type I procollagen** (PICP) in 224 patients with breast cancer (106 with bone metastases), 61 patients with prostatic cancer (30 with bone metastases), 45 patients with lung cancer (17 with bone metastases) and 13 patients with miscellaneous cancers (7 with bone metastasis) and compared the values in the presence and absence of bone metastasis. ICTP and PICP increased significantly in patients with bone metastases. By the analysis of sensitivity and specificity, the cut-off levels were considered to be 5.0 ng/ml for ICTP and 140 ng/ml for PICP. In lung cancer (bone metastases are mostly of osteolytic), ICTP was excellent marker in **detecting bone metastasis**. In breast **cancer** (**bone metastases** are mostly of mixed type), ICTP was good in **detecting bone metastases**. In prostatic **cancer** (**bone metastases** are mostly of **osteoblastic**), ICTP and PICP were good markers in **det cting** high grade of **bone metastases**. Over all, ICTP was more sensitive in the **diagnosis** of

bone metastases than PICP. However, both markers were not effective in **detecting** low grade **bone metastases**. ICTP and PICP should play a supportive role to imaging modalities in the **diagnosis** of **bone metastases**.

L12 ANSWER 8 OF 9 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 97083253 MEDLINE
DOCUMENT NUMBER: 97083253 PubMed ID: 8929827
TITLE: New and traditional serum markers of bone metabolism in the detection of skeletal metastases.
AUTHOR: Plebani M; Bernardi D; Zaninotto M; De Paoli M; Secchiero S; Sciacovelli L
CORPORATE SOURCE: Department of Laboratory Medicine, Azienda Ospedaliera di Padova, Italy.
SOURCE: CLINICAL BIOCHEMISTRY, (1996 Feb) 29 (1) 67-72. Journal code: DBV; 0133660. ISSN: 0009-9120.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970414
Last Updated on STN: 19970414
Entered Medline: 19970403

AB OBJECTIVES: The evaluation of "new" and "traditional" markers of **osteoblastic** and **osteoclastic** activity, in patients with bone metastases. DESIGN AND METHODS: Our series consist of 40 patients with clinical, radiological, and scintigraphic evidence of bone metastases, and 40 age-matched healthy subjects. In all samples, traditional markers were evaluated by measuring total alkaline phosphatase (ALP), tartrate-resistant acid phosphatase (TrACP) activity, and osteocalcin (BGP) concentration. To assess new biochemical bone markers, bone isoenzyme of alkaline phosphatase (ALP-B) activity, carboxyterminal propeptide of **type I procollagen** (PICP), and carboxyterminal telopeptide of type I collagen (ICTP) concentrations were measured. RESULTS: Our findings showed that the best diagnostic efficiency is provided by ICTP (0.94) followed by total ALP (0.90), ALP-B (0.80), and TrACP (0.76). The efficiency of BGP and PICP was, instead, very low (0.64 and 0.60, respectively). CONCLUSION: Our results confirm the utility of the new serum markers such as ALP-B and ICTP assays in **detecting bone metastases**.

L12 ANSWER 9 OF 9 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 95252053 MEDLINE
DOCUMENT NUMBER: 95252053 PubMed ID: 7734300

TITLE: Type I collagen degradation product (ICTP) gives information about the nature of bone metastases and has prognostic value in prostate cancer.

AUTHOR: Kylmala T; Tammela T L; Risteli L; Risteli J; Kontturi M; Elomaa I

CORPORATE SOURCE: Division of Urology, University of Tampere, Finland.

SOURCE: BRITISH JOURNAL OF CANCER, (1995 May) 71 (5) 1061-4.
Journal code: AV4; 0370635. ISSN: 0007-0920.

PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199506

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Last Updated on STN: 19980206
Entered Medline: 19950606

AB Although osteosclerotic bone metastases are characteristic of prostate cancer, mixed metastases with a lytic component are not uncommon. Type I collagen is synthesised by **osteoblasts** and accounts for about 90% of the organic matrix of bone. We have used new specific immunoassays for PICP (carboxy-terminal propeptide of **type I procollagen**) and ICTP (cross-linked carboxy-terminal telopeptide of type I collagen) which allow simultaneous assessment of the synthesis and degradation of type I collagen respectively. Forty patients with **bone** metastases due to prostate **cancer** at the time of **diagnosis** were investigated with these methods. Twenty-three of them had sclerotic (S) and 17 had mixed metastases with sclerotic and lytic components (S + L) as assessed by radiographs. The concentrations of PICP and ICTP in serum as well as the activity of alkaline phosphatase (AP) were increased in all patients of the S + L group, who had more aggressive bone disease and a shorter survival than the S group ($P < 0.017$). The ICTP level was above the reference range in half of the patients in the S group, whereas the PICP and AP levels were elevated in 35%. Of the bone markers, only ICTP was of prognostic significance ($P < .05$). We conclude that ICTP and PICP give information about the type and activity of the skeletal metastases. In addition, ICTP predicts prognosis.

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